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USE OF THE PHLEBOMANOMETER: NORMAL VENOUS PRESSURE VALUES AND A STUDY OF CERTAIN CLINICAL ASPECTS OF VENOUS HYPERTENSION IN MAN

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PHYSIOLOGISTS have long considered a knowledge of the variations in venous pressure essential to the proper understanding of cardiovascular physiology.[1, 2] More recently some clinicians have utilized venous pressure measurements in the differential diagnosis and clinical management of right ventricular congestive heart failure, pericardial effusion, constrictive pericarditis, cardiac tamponade, localized venous obstruction, edema, ascites, and many other clinical syndromes.[3-8] Measurements of venous pressure, however, are not often made routinely by those in the clinical fields. Furthermore, progress in a proper understanding of the pressure in veins has been retarded by many factors, principally a need for a simple, practical, portable instrument and a standardized method of recording venous pressure; and an appreciation of the clinical applications of venous pressure measurements. To date no completely satisfactory instrument for the measurement of venous pressure has been found. Such instruments have been impractical, or inaccurate, or both. A satisfactory instrument must, at least, be (1) portable, transportable, with no fluids to spill, and suitable for bedside use in the hospital or home; (2) easily sterilized and easily prepared for successive determinations; (3) suitable for use in small veins, thereby making possible comparative measurements as well as a more general use; and (4) sufficiently accurate and dependable to reveal early evidence of or change in disease.

Since a standard method of recording the venous pressure has not yet been accepted generally, values obtained by different methods are not always comparable.[9] The site taken as "heart level" varies with the various methods used.

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Any variation of this site often produces considerable differences in the results obtained. The criteria for a satisfactory heart level are discussed. Because a knowledge of the venous pressure is of diagnostic assistance in many disease states,[10] it is the purpose of this report to describe in detail the technique employed with the Phlebomanometer,[11] to discuss some of the factors affecting venous pressure, to establish a phlebostatic level and a phlebostatic axis,[12] to establish normal values of venous pressure for adults, and to present studies on patients with venous hypertension in congestive heart failure.

METHODS AND MATERIAL

The instrument used was the Phlebomanometer,[11] which consists of an aneroid type of manometer, the scale of which is calibrated in millimeters of water. The method is a direct one. By mechanically compressing a pressure bulb the pressure in the manometer system is adjusted to balance the pressure in the vein. When the balance has been accomplished the venous pressure is read from the scale of the manometer. The balance is established when a column of citrate solution in a glass adaptor comes to rest. The capillarity of the adaptors (1-mm. bore) used was 25 mm. of 2 per cent citrate solution. To correct for capillarity, the meniscus of the citrate in the adaptor was held 2.5 mm. above the level of the vein. A 23-gauge needle was usually employed, although the size of the needle did not alter the venous pressure reading, since the reading is recorded when the fluid in the adaptor is at rest. Smaller-bore needles were used when measuring high venous pressures. The Phlebomanometer conforms to the criteria established for a satisfactory venous pressure instrument.[11] It was checked at frequent intervals against a water manometer and was found to maintain its accuracy at all times.

Approximately 850 determinations were made on 200 normal subjects, and 450 determinations were made on 90 patients with cardiac disease. The normal subjects were medical students and laboratory and hospital attendants. The patients were selected from the medical wards of the Charity Hospital in New Orleans.

The subjects rested ten minutes before venous pressure determinations were recorded. In all instances consecutive readings were taken until constant readings were obtained. Particular attention was paid to the state of relaxation of the patient, the type of respiration, and the maintenance of the vein at "heart level." All determinations on normal subjects were carried out on an unpadded, level examining table with the arm abducted, slightly rotated externally, and properly supported. When the veins of other parts, such as the foot or hand, were studied, these parts were similarly supported in a relaxed state so as to avoid venous obstruction due to flexion of joints, external pressure, or constriction.

REFERENCE LEVEL OR HEART LEVEL

In order to obtain reproducible venous pressure readings, the vein under study must be placed in a constant relation to the heart. The phlebostatic

level[12] has been used as a reference level. It has the advantage of being applicable for use in positions other than the supine. It may be defined as a horizontal plane passing through the phlebostatic axis.[12] The axis is determined by the intersection of a frontal plane, passing half the distance from the base of the xiphoid of the sternum and the dorsum of the body, with a cross-sectional plane passing through the fourth intercostal space adjacent to the sternum. The use of the *phlebostatic level* of reference gives reproducible and comparable results in normal subjects when either supine, in the intermediate sitting positions or in the upright sitting position.[12] The following experiments are described in order to emphasize the practicability and reliability of the phlebostatic level as a reference level for these positions.

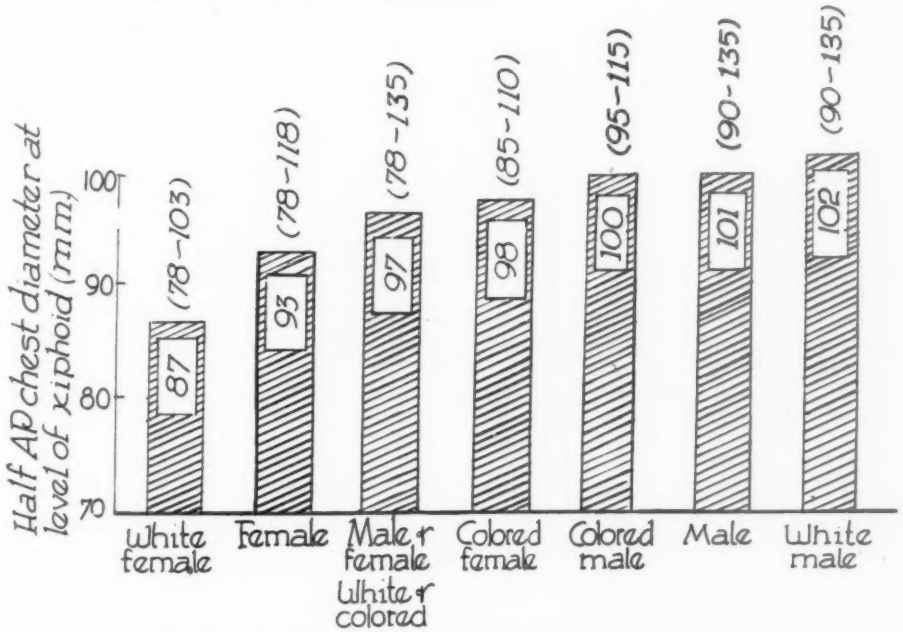

Fig. 1.—Half the anteroposterior diameter of the chest, measured from the base of the xiphoid to the table with the subject in the supine position, in 90 Negro and white males and females. A horizontal plane passing through this point forms the phlebostatic level for the supine position.

The Phlebostatic Level.—Half the distance from the base of the xiphoid to the table with the subject supine (phlebostatic level for the supine position) was measured in 90 normal subjects from 16 to 34 years of age (Fig. 1). The venous pressure was taken in the median basilic vein with the vein at this level. The subjects were divided into those with deep chests and those with thin chests. The ages, sexes, and colors of the two groups were comparable. The venous pressure did not vary significantly in the two groups.[12] The narrowest chests occurred in the white female group (average, 87 mm.; extremes, 78 to 103 mm.) and the deepest chests occurred in the white male group (average, 102 mm.; extremes, 90 to 135 mm.). The average depth of the chests for males and females of both colors was 97 mm. (extremes, 78 mm. and 135 mm.).

The influence of chest thickness on the venous pressure, using the phlebostatic level with the subjects in the supine position, was further tested in 10 subjects with very thick chests (average, 126 mm.; extremes, 110 to 135 mm.), and 10 with very thin chests (average, 89 mm.; extremes, 85 to 95 mm.) (Fig. 2). The venous pressures in the median basilic vein were 103 and 104 mm. of water, respectively. Thus even extremes of chest thickness did not materially influence the venous pressure measurements.

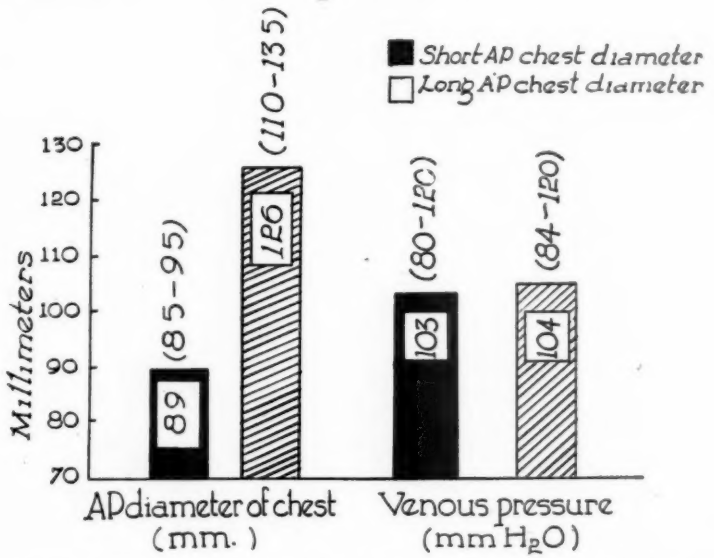

Fig. 2.—The venous pressure measured in 10 subjects with thick chests and 10 of the same sex, age, and color with thin chests. The venous pressures show no significant differences.

Venous pressures were then recorded for the median basilic vein in 13 subjects, first in the supine position, and then in the upright sitting position, the arm being raised until the pressure in the sitting position was the same as that in the supine position. In eight of the 13 subjects the vein under study fell in a horizontal plane which passed through the fourth intercostal space adjacent to the sternum. In the remaining five subjects, the vein fell either in the third or fifth intercostal space. Placing the trunk in various intermediate sitting positions and measuring the median cubital venous pressure with the vein in a horizontal plane passing through the phlebostatic axis resulted in little difference in values among normal subjects.[12] The reliability of the phlebostatic level was further tested by recording the venous pressure in a dorsal vein of the hand, with the trunk in the supine position, various intermediate sitting positions, and in the upright sitting position (Fig. 3). In all postions the hand was kept at the phlebostatic level for the supine subject. With each change of position the venous pressure increased by an amount equal to a column of blood extending from the vein under study to the phlebostatic level. Thus the phlebostatic level is a genuine physiologic level of reference.

Radiographic studies indicated that in the majority of subjects the phlebostatic axis passed through the posterior aspect of the right auricle. Thus the anatomic and physiologic reference levels coincide satisfactorily, and the phlebostatic level is a satisfactory reference level for the measurement of venous pressure for the supine position, intermediate sitting positions, and upright sitting positions.

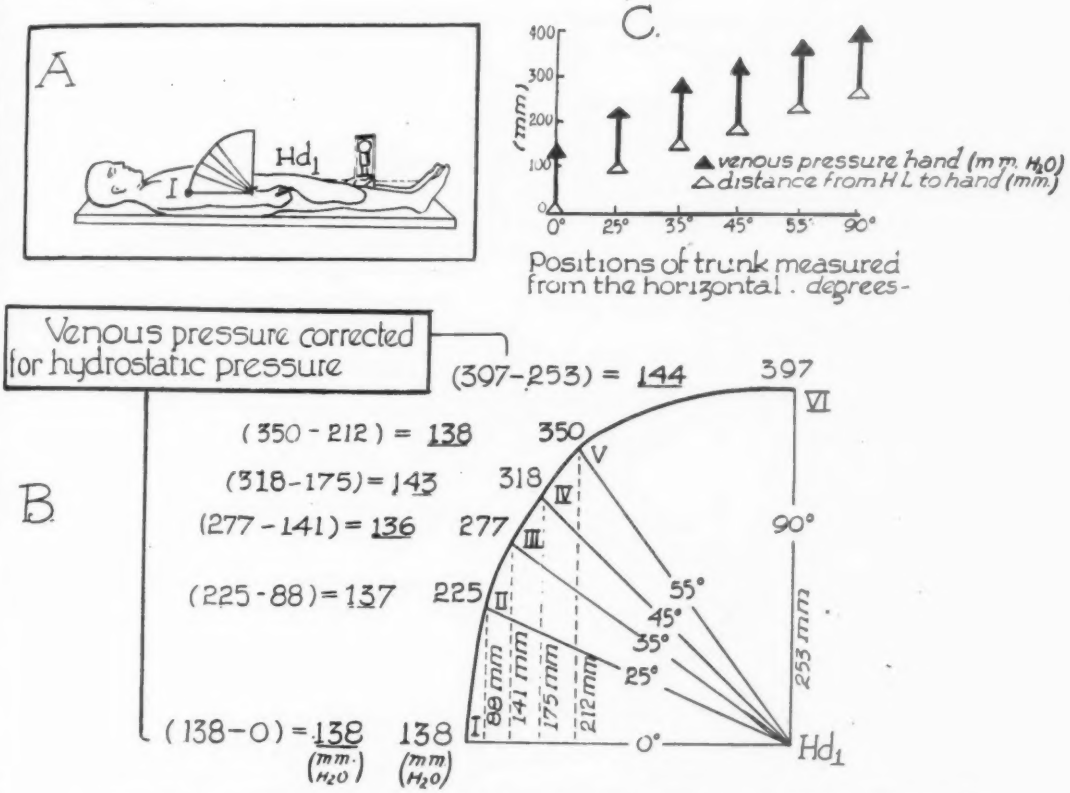

Fig. 3.—The phlebostatic axis used as heart level in the supine, various intermediate sitting, and upright sitting positions. *A*, Subject in supine position and hand (*Hd*) in a horizontal plane passing through phlebostatic axis (solid dot). *B*, Venous pressures corrected for hydrostatic pressure resulting from the elevation of the phlebostatic axis to Positions II, III, IV, V, and VI, leaving the hand in which the venous pressure determination is being made in position Hd_1. *C*, Proportional increase in venous pressure and hydrostatic pressure with each change of trunk position. The phlebostatic level is a useful reference level for subjects in the supine, intermediate sitting, or upright sitting position.

FACTORS AFFECTING VENOUS PRESSURE

Numerous factors which affect the venous pressure must be evaluated and understood if errors in venous pressure measurements are to be avoided. A knowledge of such factors is of clinical importance when measuring venous pressure.

Relation of Venous Pressure to the Phlebostatic Level.—The venous pressure was determined in the median basilic vein at the phlebostatic level in 10 subjects in the supine position. The vein was raised above and lowered below

this level and the changes in pressure were recorded. Raising the arm 100 mm. above the level reduced the pressure 100 mm. of water. Lowering the arm 40 increased the pressure 40 mm. of water. This 1:1 relationship was constant, at least for positions between 40 mm. below and 100 mm. above this level. This relationship between the phlebostatic level and the position of the vein is probably maintained for ranges wider than those studied. Thus, when venous pressure is measured in veins above or below this level a simple correction may be applied for the altered hydrostatic pressure due to the position of the vein.

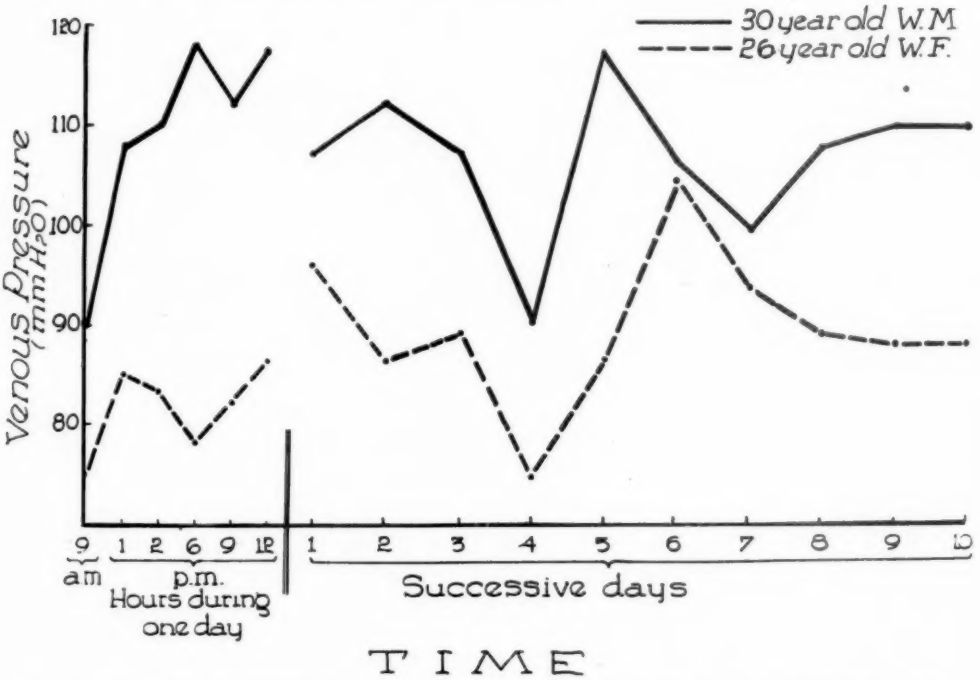

Fig. 4.—Variations in venous pressure during one day and at the same time of day for ten consecutive days.

Venous Pressure Variations During One Day and From Day to Day.—Venous pressure was determined in the median basilic vein in one man and in one woman at three-hour intervals from 9:00 A.M. to 12:00 M. throughout one day, and once daily at the same hour for ten days (Fig. 4). The error in consecutive readings was no greater than ±2.5 mm. of water. The venous pressures were generally lower in the woman than in the man. Both subjects had lower pressures in the morning than in the evening, the morning pressure being 11 mm. lower in the woman and 27 mm. lower in the man. There was no constant relationship between the venous pressure level and meals.

Ten consecutive daily recordings were made at 11:00 P.M. for ten days. The daily activity of the subjects did not vary significantly during this period. The difference between the highest and lowest readings was 29 and 27 mm. of water in the woman and the man, respectively.

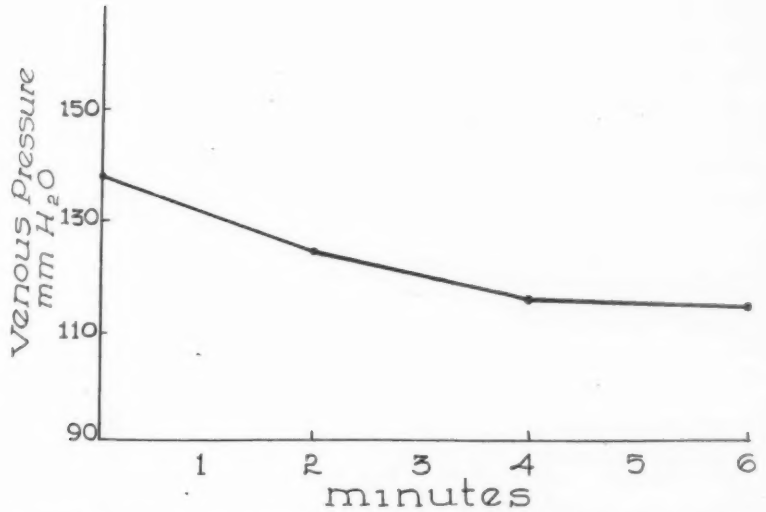

Fig. 5.—The gradual fall in the venous pressure of 20 subjects after insertion of the needle ordinarily occurred during the first four minutes.

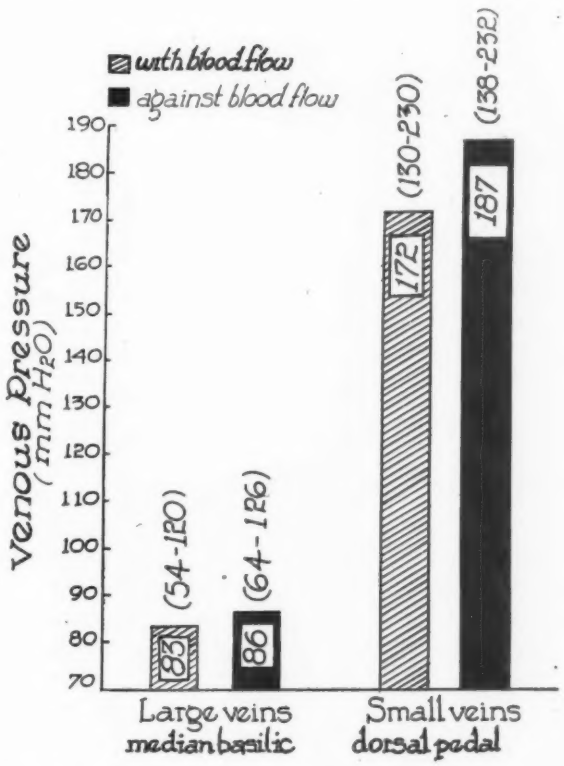

Fig. 6.—Pressures determined in large and small veins with the needle directed in and against the direction of blood flow. Pressure differences were greater in the small veins, probably because of the greater effect of venous spasm in small veins.

Venous Pressure Drift.—The venous pressure was usually high immediately after the vein was punctured, and lower after the needle had remained in place for a period of time. In the 20 subjects studied, the pressure was usually constant by the fourth minute (Fig. 5). The average decrease in pressure was 20 mm. of water. This change in venous pressure took place without apparent muscle tension or changes in respiration. Spasm of the vein was usually directly visible, particularly in the smaller veins.

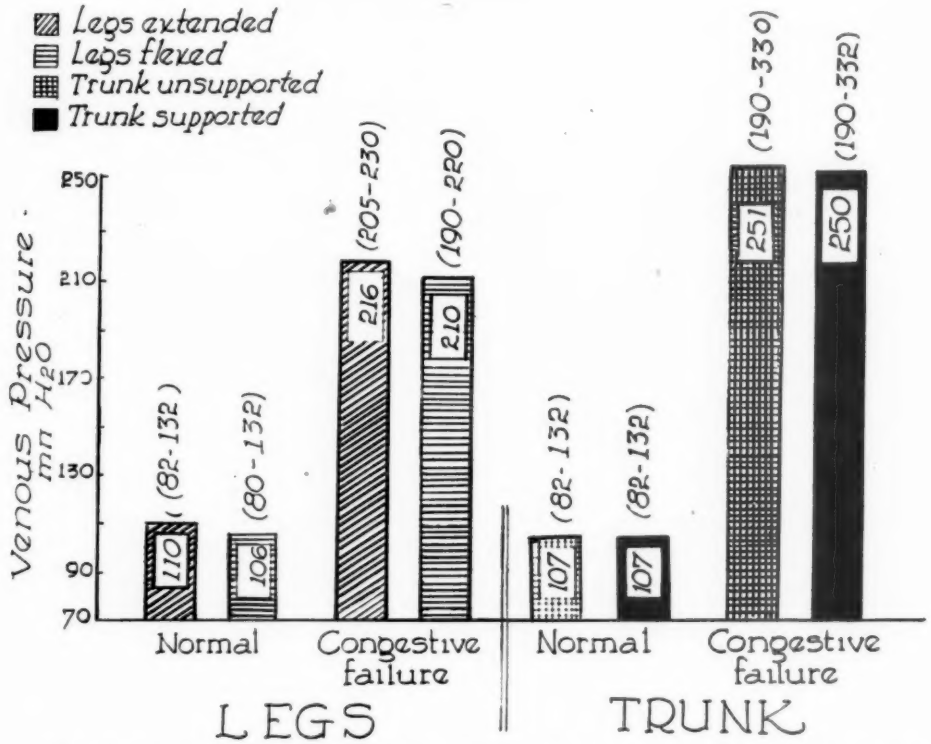

Fig. 7.—Venous pressures in 10 normal subjects and 10 patients with congestive heart failure, taken in the sitting position with the legs extended, then flexed, and with the trunk supported, then unsupported. Very few differences in pressures resulted.

Direction of Insertion of the Needle and Venous Pressure.—The venous pressure was measured in large and small veins with a 23-gauge needle, with the apex of the needle pointed first in the direction of and then against blood flow. The pressures in the median basilic vein at the antecubitus and in the greater saphenous vein at the ankle did not vary significantly with changes in needle direction. The average difference was 3 mm. of water (Fig. 6). The pressure in the small veins of the hands and feet was significantly higher (average, 15 mm. of water) when the needle was directed against the direction of blood flow. The greater differences in pressure in small veins are due to the great effects of the kinetics of flow, which are probably caused in large part by venospasm, as small veins are prone to contract tightly about the shaft of the needle and sometimes completely occlude the lumen of the vessel.

Position of the Legs and Trunk in Relation to the Venous Pressure in the Sitting Position.—Pressures in the median basilic vein were recorded in 10 normal subjects and 10 patients with right ventricular congestive heart failure (Fig. 7). Pressures were recorded with the subject sitting with the legs extended and with the legs flexed, the feet always being lightly supported. In both groups the pressures were slightly lower with the legs flexed. The pressure was then measured in the same individuals, sitting, with the trunk unsupported, then with the trunk supported by a backrest. The differences in venous pressures did not exceed 1 mm. of water under the latter conditions.

Respiration and Venous Pressure.—Certain statements can be made concerning the relationship between venous pressure and the phases of respiration. A 20-gauge needle was used to record the respiratory effects. The venous pressure fell slightly with normal quiet inspiration and rose with quiet expiration. Slow, deep inspiration greatly reduced the antecubital venous pressure, and slow deep expiration markedly increased it. The Valsalva experiment increased the pressure still more and the Müller experiment decreased it. Rapidly repeated deep inspirations caused a more marked fall in pressure than did one single deep inspiration. It is well to remember that the normal respiratory changes were often markedly altered in patients with venous hypertension (vide infra).

Muscle Tension and Venous Pressure.—Venous pressures were recorded in the veins of the arms and legs of ten subjects before and during muscle contraction. No difference in pressure was found in the median basilic vein. Tension of the muscles on the lower extremity sometimes resulted in a considerable increase in the pressures in the greater saphenous vein (average difference, 20 mm. of water). This increase may be due to obstruction of the deep veins of the legs, which places a greater load on the superficial veins in which the measurement is being made. It is possible that in unusually muscular individuals muscle tension in the arms may increase the pressure by the same mechanism.

ESTABLISHMENT OF NORMAL VALUES

Normal values for venous pressure were determined in 130 normal young adult male and female, Negro and white subjects. All measurements were made in either the supine or sitting position with the vein at the phlebostatic level.

Normal Values for the Median Basilic Vein of Adults in the Supine Position.—The pressures were recorded in the veins of the right and left arms of 70 subjects (Fig. 8). The pressures in the two arms did not differ, on an average, by more than 2 mm. of water in any group studied. The lowest pressures were encountered in the white females (average, 90.5 mm.; extremes, 80 to 116 mm. of water), and the highest pressures were encountered in the Negro males (average, 103.5 mm.; extremes 66 to 128 mm. of water). The average for both Negro and white females was 100.5 mm. of water. The highest value for the females was 128 mm. of water, and for the males 140 mm. of water. The average value for the entire group was 97 mm. of water, the range being 50 to 140 mm. of water.

Normal Venous Pressure Values for Various Veins of the Body in the Supine and Sitting Positions.—Venous pressures were recorded in various veins of the body in 100 subjects (Fig. 9). No significant difference between the pressures of the right and left sides of the body (arms or legs) was noted. The average pressures in the median basilic, femoral, and dorsal metacarpal veins,

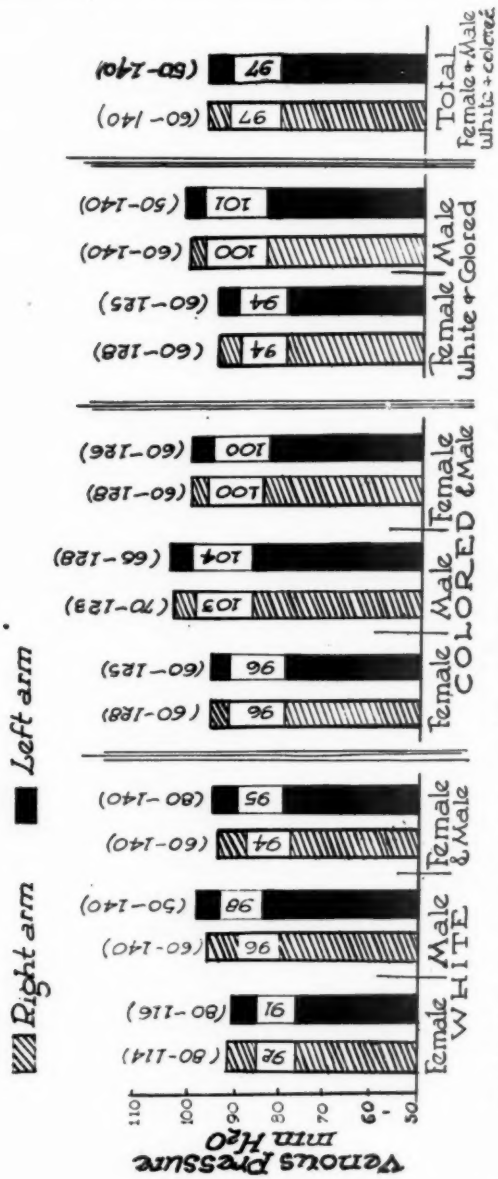

Fig. 8.—Venous pressures in the right and left arms in males and females and Negro and white subjects in the supine position. The average pressure for the group is 97 mm. of water, and the range is 50 to 140 mm. of water.

in the great saphenous vein at the ankle, and in the dorsal pedal veins were 97, 111, 120, 149.5, and 175.5 mm. of water, respectively. The ranges of pressure for these vessels were 50 to 140, 98 to 128, 70 to 146, 110 to 190, and 124 to

210 mm., respectively. Numerous venous pressure determinations in various veins in one subject are shown in Fig. 10.

The venous pressure in a dorsal metacarpal vein was compared with that in a median cubital vein in 20 sitting subjects (Fig. 11). There was an average difference of 26 mm. of water in the pressure of the veins of the elbow and hand in the sitting position, as compared with an average difference of 23 mm. of water in the pressure of these veins in the supine position. The pressures in the veins of the hands were always higher.

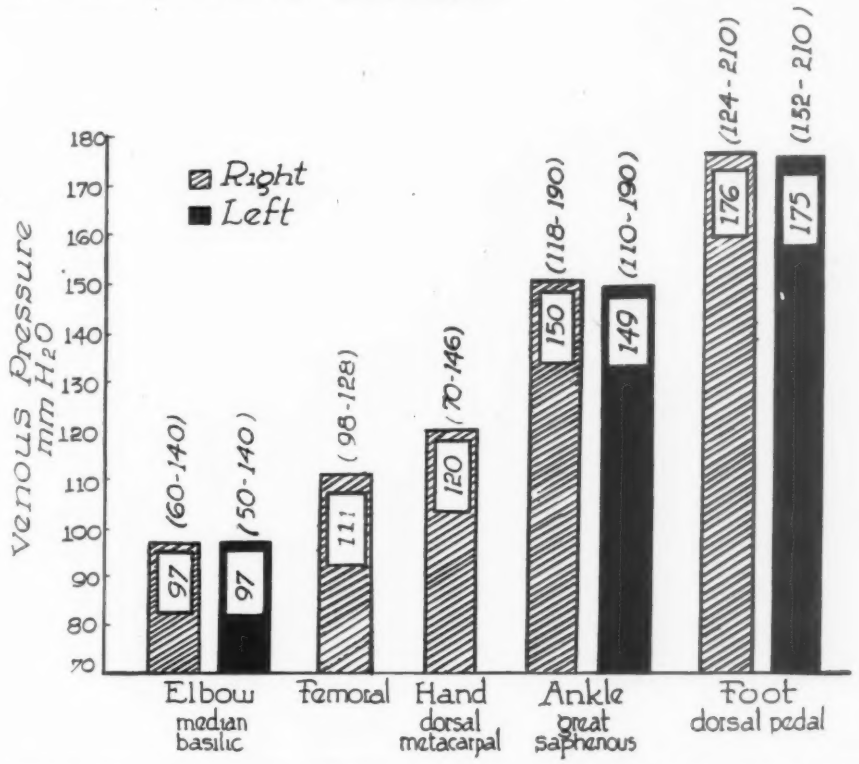

Fig. 9.—Venous pressures in 100 Negro and white subjects of both sexes. The pressures were taken in various veins of the body. In general, the greater the distance from the heart, the higher the venous pressure.

VENOUS PRESSURE IN PATIENTS WITH RIGHT VENTRICULAR CONGESTIVE HEART FAILURE

The following experiments illustrate some of the differences in venous pressure between normal subjects and 50 patients with cardiac disease with and without congestive heart failure.

Venous Pressure in the Supine and Sitting Positions.—The pressures in the median basilic veins in the supine and sitting positions were compared in 40 normal subjects and in 30 patients with Class I, Class III, or Class IV heart disease (Fig. 12). In the normal group the pressures in the supine and sitting positions showed no significant difference, being 3 mm. of water greater for the

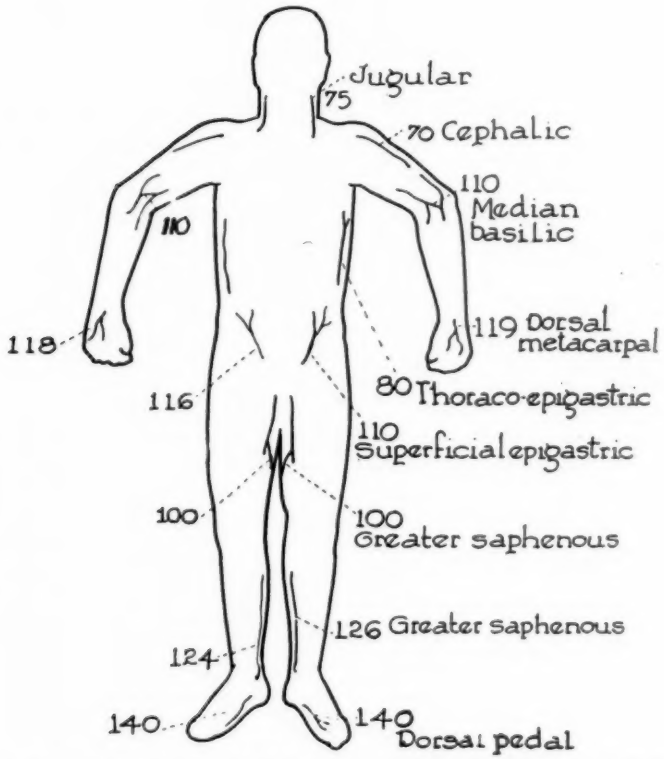

Fig. 10.—Venous pressures in various veins of one individual showing gradient of pressures from the periphery to the heart.

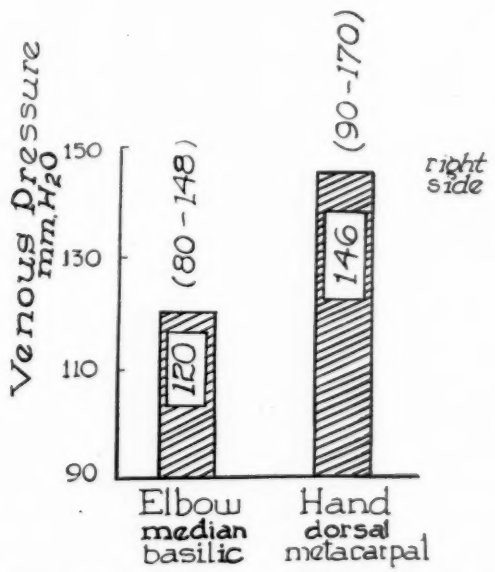

Fig. 11.—Venous pressures in the median cubital and dorsal metacarpal veins of 20 subjects in the sitting position. These values are not significantly different from the pressures in these veins with the subjects in the supine position.

supine position. In patients who were placed in Class I, that is, patients without clinical evidence of failure, the average pressure in the sitting position was 4 mm. of water less than that in the supine position. Patients with congestive heart failure who were placed in Class III or IV had venous pressures which were 76 mm. of water lower in the sitting than in the supine position. The

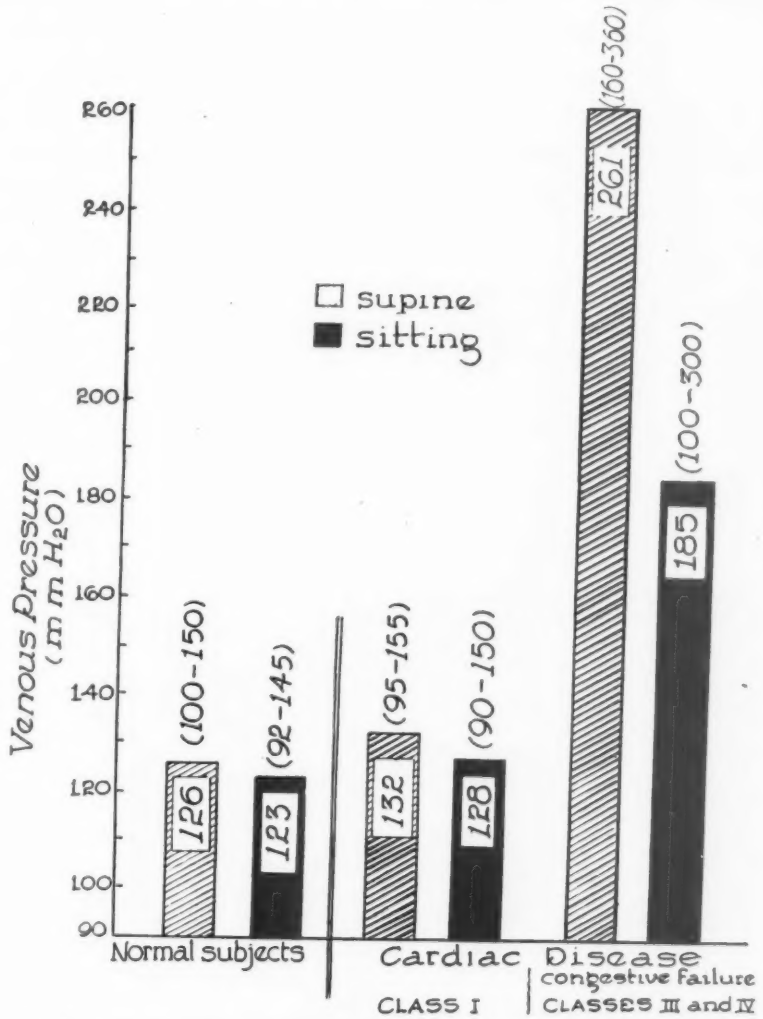

Fig. 12.—Venous pressures of 60 normal subjects and 50 patients with cardiac disease. These pressures were recorded in the median cubital vein, using the phlebostatic level for reference, with the subjects first in the supine position and then in the sitting position. The pressure recorded with the patient in the supine position was a better indication of the presence of congestive failure than was the pressure recorded with the patient in the sitting position.

average pressure in the supine position was 261 mm. of water, and in the sitting position 185 mm. of water. All the patients in Class IV had venous hypertension in the supine position, that is, a venous pressure greater than 140 mm. of water. However, 30 per cent of these patients had normal venous pressures in the sitting position.

Effect of Abdominal Compression on Venous Pressure.—The pressure in the antecubital vein was recorded in 40 normal supine subjects and 30 supine patients with varying degrees of cardiac disease with and without congestive heart failure (Fig. 13). Pressure was then manually applied over the umbilicus for a period of one minute.[13] The region of the abdomen compressed

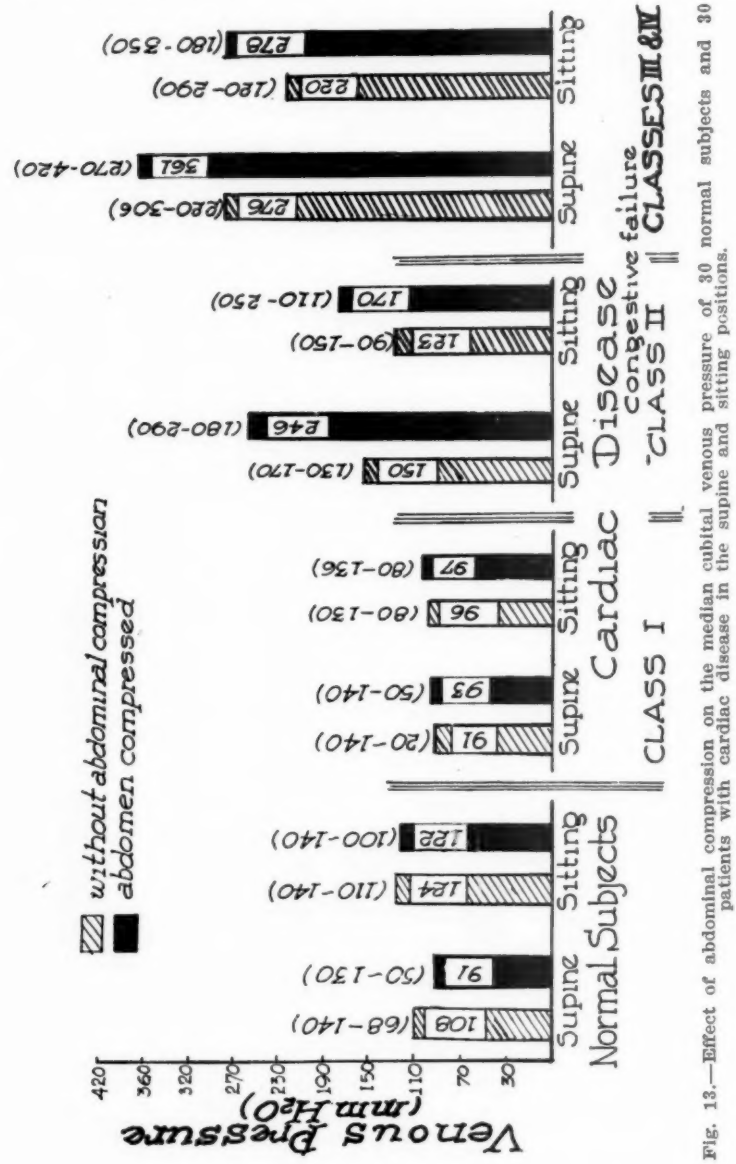

Fig. 13.—Effect of abdominal compression on the median cubital venous pressure of 30 normal subjects and 30 patients with cardiac disease in the supine and sitting positions.

was not important, since it was found that pressure exerted over the liver and over various other regions of the abdomen did not alter the results (vide infra). In all instances the patients were instructed to breathe naturally. Compression

of the abdomen of normal subjects resulted either in a fall in the venous pressure or in no change (Fig. 13). The average pressure before compression was 108 mm. of water; that during compression was 91 mm. of water, an average fall of 17 mm. of water. In the sitting position the average difference between the pressure before and that during compression was –2 mm. of water. In 30 per cent of these latter patients the pressure rose to + 10 mm. of water or less with abdominal compression.

In 10 patients with heart disease without failure (Class I) the results were essentially the same as for the normal subjects. The average pressure in the median basilic vein before abdominal compression, with the patient supine, was 91; during compression it was 93 mm. of water. Venous pressures before and during abdominal compression in the sitting positions were 96 and 97 mm. of water, respectively (Fig. 13).

In 10 patients with cardiac disease (Class II, mild congestive heart failure), the venous pressure in the supine position was only slightly greater than normal, averaging 150 mm. of water, and varying from 130 to 170 mm. of water. Abdominal compression produced a rise in pressure to an average of 246 mm. of water, an average increase of 96 mm. of water. Abdominal compression produced an average increase in pressure in these patients when sitting of 47 mm. of water (Fig. 13).

In cardiac patients resting in the supine position (Class III and IV, marked congestive heart failure), the average venous pressure before abdominal compression was 276 mm. of water and during compression 361 mm. of water, an average difference of 85 mm. of water. In the sitting position the pressure before abdominal compression was 220 mm. of water and that during compression was 278 mm. of water, an average difference of 58 mm. of water.

From these experiments it would seem that abdominal compression in supine patients with normal or borderline venous pressures is particularly useful in the diagnosis of early congestive heart failure.

Venous Normotension, Venous Hypertension, and Certain Clinical Findings in Patients With Congestive Heart Failure.—Clinical findings and venous pressures were recorded in 20 patients with heart disease, all of whom had clinical heart failure. From these data the following conclusions may be drawn: (1) Venous hypertension does not always exist even though other signs of right, left, or right and left ventricular congestive heart failure may be present. (2) Even though physical signs of right ventricular congestive failure are not striking, the venous pressure may be high if the pressure is recorded during rapidly progressing failure. (3) The venous pressure may be normal when other signs of right ventricular congestive failure are present, if the pressure is recorded during rapidly improving failure. Thus in some instances the venous pressures were within normal limits even in the presence of hepatomegaly, ascites, and edema of the legs. (4) When the antecubital venous pressure was 220 mm. of water or greater, the liver was always found to be enlarged. (5) When the pressure reached 250 mm. of water, ascites, leg edema, and orthopnea were always present.

DISCUSSION

The venous pressure in both healthy and diseased patients may be accurately determined by the Phlebomanometer, with an error not greater than ±5 mm. of water. Careless determinations may result in gross inaccuracies. The most important sources of error were: (1) venous obstruction produced by kinking of veins, (2) breath-holding, (3) muscle contraction, (4) insufficient attention to the problem of heart level,[14] (5) temporal variations, (6) spasm of veins, and (7) direction of insertion of the needle. To eliminate many of these sources of error the following procedure is advocated: Before a measurement is made, the subject should rest supine for ten minutes, with the arm placed at the phlebostatic level and abducted sufficiently to form an angle of approximately 60 degrees with the body. Clothing likely to produce venous obstruction should be loosened. Holbrook[15] has shown that abduction of the arm to 90 degrees, as well as more marked abduction, produces abnormally high readings. Brandt and Katz[16] found that abduction of the arm affects the anatomic relationship of the clavicle, first rib, and subclavian vein so as to exert pressure on the axillary and subclavian veins. The respirations should be watched to prevent sighing or breath-holding. Consecutive readings should be recorded until constant readings are obtained. It is desirable to make the measurement on a firm, flat table with the head of the subject on a low pillow. The use of a level and ruler may be employed for most accurate work but this is not necessary for most clinical purposes.

The choice of heart level is important in order to avoid great variations in results. A study of the literature showed great variation[17-40] in the points of reference and normal valves for the antecubital vein obtained by direct methods for the supine position (Table I). The marked variations in normal values resulted chiefly from differences in the reference levels used as heart level. The normal range for the venous pressure with the phlebostatic level at the so-called heart level for the antecubital vein is 50 to 140 mm. of water. These values compare favorably with the normal values obtained by others using a constant heart level fixed 100 mm. from the table, as well as with measurements using the midaxillary line as the level of reference.[8, 39, 40] It is desirable to have a level which cannot be used only for the supine position, but also for the upright sitting and intermediate sitting position. These and previous studies by the authors[12] indicate that a horizontal plane passing through an axis running between the lateral surfaces of the trunk half the distance from the anterior and posterior aspects of the body, at the level of the fourth intercostal space anteriorly, presents a suitable reference line or level from which to measure the venous pressure with the trunk in any of the afore-mentioned positions. Normally there is no significant difference in the venous pressure in the supine, intermediate sitting, or upright sitting position if the pressure is measured with the vein at the phlebostatic level. In the sitting position the trunk may be either supported or unsupported and the legs may be extended or flexed without significantly altering the antecubital venous pressure.

The applications of venous pressure determinations to clinical practice are numerous and are particularly useful in the diagnosis of right ventricular congestive heart failure, constrictive or effusive pericarditis, venous obstruction, and edema. In patients with congestive heart failure the venous pressure with the patient in the supine position was a much more reliable indication of failure than was the venous pressure taken in the sitting position. Abdominal compression was also a valuable aid in the diagnosis of congestive heart failure.[13] The response to abdominal compression was abnormal in approximately 30 per cent of the patients whose antecubital venous pressure, taken when they were in the supine position, was normal or borderline. The compression procedures may be executed in the supine or sitting position. They are somewhat more sensitive in the former. The average rise in pressure of patients with Class II heart function (mild congestive failure) during compression was 96 mm. of water when supine and 47 mm. of water when sitting.[41, 42] In the normal supine subject abdominal compression produced either a fall or no change in pressure in the median basilic vein (average was a fall of 17 mm. of water). In the sitting position, abdominal compression sometimes produced a rise in pressure of as much as 10 mm. of water (average was a fall of 2 mm. of water).

The mechanism of fall in venous pressure in the normal subjects is unknown. It is conjectured that abdominal compression interferes with venous return through the inferior vena cava. This results in a drop in venous pressure in the upper extremities and a rise in the lower extremities. In right ventricular congestive heart failure, abdominal compression probably forces blood from the already engorged venous reservoirs of the abdominal cavity into the thorax, which, in the presence of an inefficient heart, results in an increase in the pressure in the veins of the upper extremities. Similar results have been noted in the presence of pericarditis with marked effusion.[13] Abdominal compression, when carried out in patients with ascites from causes other than heart failure produced no increase in the venous pressure in the antecubital vein.

When the antecubital venous pressure was recorded for the supine position and the arm was elevated 90 degrees, that is, perpendicular to the table, the pressure in normal patients fell markedly and approached atmospheric pressure. In the presence of marked congestive failure with an already elevated venous pressure, the pressure fell the same amount as in the normal subject, but remained considerably above atmospheric pressure. In normal subjects this phenomenon may be due to partial collapse of the vein, and in those with congestive failure to the inability of the overfilled vein to collapse. Abdominal compression, particularly when carried out in the supine position, reveals evidence of failure much earlier than does the finding of an elevated pressure after elevation of the arm.

In correlating the venous pressure with the clinical picture of failure it was noted that the pressure may be either high or normal in the presence of clinical signs of failure, depending upon whether the edema is increasing or decreasing. It would seem that an increase in venous pressure precedes the onset of the clinical manifestations of failure. When the pressure reached 250 mm. of water hepatomegaly, ascites, edema, and orthopnea were always present.

It must be remembered that these studies were conducted in patients who had had absolute bed rest, in a partially sitting position, with legs extended, for some days. These generalizations may not be entirely applicable to patients in other positions, such as the sitting position with legs down.

SUMMARY

A method of use of the Phlebomanometer was described. The phlebostatic level was defined as a horizontal plane passing through the phlebostatic axis which results from the intersection of a frontal plane passing half the distance from the base of the xiphoid to the dorsum of the body and a cross-sectional plane passing through the fourth intercostal space adjacent to the sternum. The use of the phlebostatic level as a level of reference gives comparable results in normal subjects in the supine, intermediate sitting, or upright sitting position.

Certain factors affecting the venous pressure were discussed. The pressure fell when the vein under study was raised above the phlebostatic level, and it increased as the vein was lowered below this level, the changes being equivalent to the hydrostatic effects. Venous pressures were higher in males than in females and in both sexes they were higher in the morning than in the evening. In one instance the morning-evening difference was 27 mm. of water. Venous pressures taken daily at a certain hour varied as much as 29 mm. of water. The venous pressure was higher immediately after inserting the needle into the vein, and fell to a constant level in four minutes. The venous pressure was ordinarily higher when the needle was inserted against the direction of blood flow than when it was inserted in the direction of flow. This difference was slight in the large veins, but was marked in the small ones, probably because of the greater effect of venous spasm in small veins.

Venous pressures taken in the median antecubital veins with the subjects in the sitting position were essentially the same with the trunk supported as with the trunk unsupported, and with the legs extended as with the legs flexed.

The pressure normally rose with expiration and fell with inspiration. The pressure was increased by the Valsalva experiment and decreased by the Müller experiment. Muscle tension of the legs increased the pressure in the greater saphenous vein at the ankle but did not increase the median antecubital pressure.

The average normal antecubital pressure in females (Negro and white) was 94 mm. of water, and in males (Negro and white), 100.5 mm. of water. The range of normal for both Negro and white males and females, in the median antecubital veins with the subject supine, was 50 to 140 mm. of water. Average normal pressures in the median basilic, femoral, and dorsal metacarpal veins, in the great saphenous vein at the angle, and in the dorsal pedal veins were 97, 111, 120, 150, and 178 mm. of water, respectively.

In patients with congestive failure the venous pressure taken in the supine position was a better index of failure than was the pressure in the sitting position, since the pressure with the patient supine was often elevated when the pressure with the patient sitting was normal.

In normal subjects resting in the supine position, compression of the abdomen ordinarily produced a fall in the antebrachial venous pressure, but usually produced a rise in this pressure when right ventricular congestive heart failure was present. Abdominal compression sometimes gave evidence of congestive failure when the venous pressure with the patient supine was within normal limits.

A correlation of the clinical signs and symptoms of congestive heart failure with the level of the venous pressure showed that, when the venous pressure was 250 mm. of water, ascites, leg edema, orthopnea, and hepatomegaly were always present in hospital bed patients with congestive failure.

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HEMODYNAMICS OF ACUTE HEMORRHAGE IN MAN

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THE adjustments of the circulation to acute hemorrhage have been extensively studied in experimental animals. A complete hemodynamic study of the effects of acute hemorrhage in man has been difficult because of the lack of a method for measuring the cardiac output and the right atrial pressure in acutely ill patients. The development of the technique of right atrial catheterization, as described by Cournand and Ranges,[1] made clinical studies of acute hemorrhage possible. The purpose of this paper is to describe the hemodynamics in thirteen patients with acute blood loss.

METHODS

The cardiac output was measured by the utilization of the Fick principle. An inlying catheter in the right atrium, introduced by way of the antecubital vein, was used for measuring the pressure and obtaining samples of blood. A special needle was introduced into the femoral artery through which pressures were measured and blood samples were obtained. The mean right atrial pressure was measured with a manometer commonly used to measure venous pressures, the point of reference being 5 cm. posterior to the fourth costochondral junction.

Blood samples for oxygen analyses were collected under oil and analyzed by the method of Van Slyke.[2] The oxygen consumption was determined by the analysis of a two- or three-minute sample of expired air, using the method of Haldane. The femoral arterial pressure was recorded optically by the method of Hamilton.[3] The mean arterial pressure was measured by planimetric integration of the area beneath the tracing. The peripheral resistance was calculated by the formula:

$$R = \frac{\text{Pm (mean pressure in mm. Hg)} \times 1332}{\text{C.O. (cardiac output in ml. per sec.)}}$$ [4]

Hemoglobin concentration was measured with a photoelectric colorimeter. Heparin was used as the anticoagulant to determine the hematocrit reading. The plasma volume was measured by the injection of the dye T 1824. Concentra-

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TABLE I. DATA ON THIRTEEN SUBJECTS WITH ACUTE HEMORRHAGE

PATIENT	DIAGNOSIS	AGE	SEX	SURFACE AREA	OXYGEN CONSUMPTION	ARTERIAL OXYGEN CONTENT	MIXED VENOUS OXYGEN CONTENT	ARTERIOVENOUS OXYGEN DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	HEMOGLOBIN	HEMATOCRIT	FEMORAL ARTERIAL PRESSURE			PULSE RATE	PERIPHERAL RESISTANCE	TOTAL PROTEIN	ATRIAL PRESSURE	BLOOD VOLUME	BLOOD ALCOHOL†
													SYSTOLIC	DIASTOLIC	MEAN						
		YRS.		SQ. M.	C.C. PER MIN. PER SQ. M.	VOLUMES PER CENT			L. PER MIN.	L. PER MIN. PER SQ. M.	GM. PER 100 C.C.		MM. HG			BEATS PER MIN.	ABSOLUTE UNITS	GM. PER 100 C.C.	MM. H_2O	PER SQ. M.	MG. PER 100 C.C.
C. J.	Laceration	39	M	1.76	127	14.9	6.8	8.1	2.8	1.6	12.1	36	61	33	41	68	1,162	5.8	10		
A. D.	Laceration	33	F	1.64	112	11.9	5.7	6.2	2.7	1.7	9.8	33	68	43	53	107	1,560	5.4	5		180
W. T.	Laceration	52	M	1.76	90	14.5	9.4	5.1	3.1	1.8	12.0	36	87	53	63	84	1,623	5.6	-20	2,110	160
R. E.	Bleeding from peptic ulcer	24	M	1.53	183	16.0	5.5	10.5	2.7	1.8	11.8	40	88	79	82	107	2,427		-20	2,290	
C. W.	Laceration	40	M	1.86	114	12.4	6.7	5.7	3.7	2.0	10.0	31	84	50	59	88	1,270	5.1	5		
M. Z.	Laceration	22	F	1.46	111	11.9	6.8	5.1	3.2	2.2	10.2	32	86	47	59	72	1,480	5.8	5	1,820	
L. A.	Laceration	15	M	1.68	113	13.1	8.1	5.0	3.8	2.3	10.1	33	89	58	70	88	1,473	4.9	0	2,040	
E. M. B.	Laceration	30	F	1.39	117	12.0	7.4	4.6	3.5	2.5	9.3	27	92	55	65	92	1,485	5.2			247
C. F.	Laceration	40	M	1.79	131	12.6	7.7	4.9	4.8	2.7	10.4	35	90	46	65	94	1,082	5.5	20		221
L. D.	Laceration	26	M	1.60	136	16.7	11.9	4.8	4.5	2.8	12.7	38	91	65	69	96	1,225	5.6	15	2,330	348
H. F.	Laceration	45	M	1.68	116	14.5	10.7	3.8	5.1	3.1	11.1	36	90	56	68	88	1,065	5.6	20	2,320	180
O. M.	Bleeding from peptic ulcer	33	M	2.0	187	11.6	6.6	5.0	7.5	3.8	9.5	28	94	61	71	136	760	4.7	-15		
J. E.	Laceration	29	F	1.66	130	10.8	8.2	2.6	8.3	5.0	9.3	27	92	60	74	125	710	4.5	- 5	1,760	
Averages of those with cardiac index 1.6 to 2.5					121			6.3		2.0			82	52	62	88	1,560		- 2	2,070	
Averages of those with cardiac index 2.7 to 5					140			4.2		3.5			91	58	69	108	970		+ 7	2,140	
Average of normals*					128			4.0		3.3			124	67	85	68	1,160		31		

*Reference 6.

†The blood alcohol determination was not made if there was no clinical evidence of alcoholism.

tions in serial blood samples were determined with a Beckmann spectrophotometer. Blood alcohol concentrations were determined by the method of Harger[5] whenever there was any clinical evidence of alcoholism.

RESULTS

Observations were made on 13 patients with acute blood loss (Table I). In 11 patients hemorrhage was the result of knife wounds. These patients were brought immediately to the hospital and studies were usually begun within an hour. The other two patients had bleeding into the gastrointestinal tract from a peptic ulcer. In none did the circulation appear normal. The systolic arterial pressure was below 100 mm. Hg in each instance. The hemorrhage was acute in the majority of the patients, and complete hemodilution had not occurred. In nine patients the hemoglobin level was 10 Gm. or more per 100 c.c.; in four the level was between 9 and 10 Gm. The plasma volume was measured in seven patients and was found to be below the expected normal level in each instance.

The cardiac output values are difficult to compare with those of control subjects because the cardiac output normally varies with the size of the subject. For this reason we will compare the cardiac index (output in liters per minute per square meter of body surface) of patients with hemorrhage with the cardiac index of normal subjects.

The cardiac index of normal young males in the basal state in our laboratory averaged 3.3, with a range of 2.3 to 4.1.[6] The patients with hemorrhage were brought in from the street, usually in the evening, and were not basal. Many of them were restless and in five subjects the situation was complicated by acute alcoholism. Had it not been for the blood loss, the average cardiac index in this group would certainly have exceeded that of our basal subjects. We have assumed that cardiac output was inadequate in all patients in whom the cardiac index was below 2.6 and that it was probably inadequate when the index was below 3.

In the five patients with the cardiac index ranging from 2.7 to 5, the clinical signs and symptoms of mild shock were present. The atrial pressure tended to be low and the mean arterial pressure was decreased. The average arteriovenous oxygen difference was 4.2 volumes per cent (normal, 4), and the average cardiac index was 3.5 (normal, 3.3). The peripheral resistance tended to be low.

The cardiac index was below 2.6 in eight patients. These patients presented the typical clinical picture of circulatory failure. The oxygen consumption was not decreased. The arteriovenous oxygen difference was considerably increased. The systolic, diastolic, and mean arterial pressures were greatly lowered. The atrial pressures were low, but not significantly lower than in the group with a higher cardiac index. The peripheral resistance was never decreased. The average was 1,560, as compared with 1,160 in the control group. The peripheral resistance was not related to the level of the blood alcohol. The heart rate varied from 68 to 107 beats per minute. There was no correlation between the degree of reduction in cardiac output and the heart rate.

Restoration of the blood volume with physiologic salt solution, human albumin solution, whole blood, or gelatin solution resulted in an increase in cardiac output, atrial pressure, and arterial pressure. The peripheral resistance usually fell sharply. The heart rate either decreased, increased, or showed no change.

DISCUSSION

The sequence of events which occur when blood is removed from the body can now be described in more detail as the result of the data reported in this paper and in other recent contributions to the literature.

The removal of from 400 to 900 c.c. of blood causes a fall in atrial pressure without any other significant finding except a slight rise in heart rate.[7] The same results are obtained when blood is pooled in the extremities by venous tourniquets.[7] The results obtained by the catheter technique have been confirmed in our laboratory by the ballistocardiograph and support the conclusions drawn from the ballistocardiographic studies reported by Starr and his coworkers.[8] They are at variance with the results of McMichael and Sharpey-Schafer,[9] who measured the cardiac output by the catheter technique after venisection and found an almost linear relationship between the fall in atrial pressure and the decrease in cardiac output.

The patients reported here had lost sufficient blood to cause circulatory insufficiency and represent a more advanced stage of blood loss than had been produced in this laboratory by the removal of blood from volunteer donors.[7] The atrial pressure was found to be lower than that in the control group, but not lower than that in the donors who had been bled or in the normal subjects who had blood pooled in their extremities from the application of venous tourniquets.[7]

The fact that no further lowering of the atrial pressure was found in these subjects with severe circulatory failure is of interest. That the circulatory deficiency was the result of a decrease in blood volume was amply demonstrated by the results of therapy. Increasing the blood volume uniformly increased the cardiac output. It may be that the relationship between the blood volume and atrial pressure is not linear. Under these circumstances the removal of the first few hundred cubic centimeters of blood would cause a greater and more obvious fall in atrial pressure than would the subsequent removal of equal amounts. The mean atrial pressure as measured with a water manometer may not reflect the actual variations in atrial pressure throughout the heart cycle. Changes in pleural pressure may have masked a decrease in effective atrial pressure. The problem needs further investigation.

Patients who are injured may have reflex vasodilatation with the picture of acute circulatory collapse. In this condition the peripheral resistance falls to a low level without a corresponding fall in cardiac output or atrial pressure.[10] Reflex vasodilatation may well have accounted for a lowering of the arterial pressure in certain patients reported in this paper. In all of the patients with a cardiac index below 2.6 the peripheral resistance was normal or high, indicating that reflex vasodilatation had played no part in the low arterial pressure. The

findings are similar to those reported in dogs and indicate at least normal arteriolar constriction in this stage of hemorrhagic shock.[11]

In these patients hemodilution was not completed at the time the observations on the circulation were made. When anemia becomes more marked the picture is somewhat more complicated because the heart must pump more of the anemic blood to supply the body needs.[12] During the acute stage of blood loss the circulation becomes steadily smaller. As hemodilution occurs and anemia develops the cardiac output will rise to the normal level. If the hemodilution continues the anemia will stimulate the heart to pump more blood and the circulation will become hyperactive. This sequence of events may be seen in a short period of time if plasma or albumin is given and immediate hemodilution accomplished.

CONCLUSIONS

1. Studies of the hemodynamics were made in 13 patients with circulatory insufficiency resulting from acute blood loss. Right atrial catheterization was employed to secure mixed samples of venous blood and measure the mean right atrial pressure. The cardiac output was calculated utilizing the Fick principle. The femoral arterial pressure was recorded optically.

2. In all of the patients the femoral arterial pressure was below 100 mm. of mercury. Complete hemodilution had not occurred and the blood volume was decreased at the time of the study.

3. In the five patients with cardiac index above 2.6, signs and symptoms of mild shock were present. The arterial and atrial pressures were decreased, but the cardiac output, arteriovenous oxygen difference, and the peripheral resistance were within the normal or low normal range. Reflex arteriolar dilatation may well have accounted in part for the low arterial pressure.

4. In the eight patients with cardiac index below 2.6, the circulation was definitely abnormal. The arteriovenous oxygen difference was increased, the atrial and arterial pressures were low. The peripheral resistance of the group as a whole was elevated.

5. An increase in blood volume by the use of intravenous fluid always caused a rise in atrial and arterial pressures, an increase in cardiac output, and a fall in peripheral resistance.

6. Circulatory failure from hemorrhage may be complicated by reflex vasodilatation as occurs in the common faint. If it is uncomplicated by this factor, it is not associated with arteriolar dilatation during the first few hours.

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THE CIRCULATION IN PENETRATING WOUNDS OF THE CHEST: A STUDY BY THE METHOD OF RIGHT HEART CATHETERIZATION

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PENETRATING wounds of the chest are frequently associated with profound circulatory disturbances. On admission to the hospital patients with such chest wounds present a striking clinical picture characterized by restlessness, sweating, cold extremities, and weak, thready pulse. They appear so acutely ill that the administration of fluid by vein is usually begun immediately. In all cases, the condition is complicated by some degree of hemorrhage, either external or into the pleural space. The majority of these patients improve in a short time and characteristically have no further circulatory difficulty unless they continue to bleed internally. It was impossible to decide on clinical grounds whether the circulatory collapse was the result of blood loss alone or the result of some other mechanism related to the wound in the pleura and lung.

In order to understand more clearly the state of the circulation in these patients, quantitative hemodynamic data were collected on thirteen patients with penetrating wounds of the pleura.

METHODS

The techniques used in this study have been described elsewhere.[1, 2] The right atrium was catheterized to obtain samples of mixed venous blood and to measure the right atrial pressure. The arterial pressure was recorded optically from a needle placed in the femoral artery.

The cardiac output is recorded as the cardiac index which is the output of the heart per minute per square meter of body surface. The use of the cardiac index facilitates the comparison of data between subjects of different height and weight.

RESULTS

Thirteen patients with chest injuries were studied (Table I). Ten patients received their injuries from knives, two from bullets, and one as a result of multiple fractured ribs. Eleven of these had blood within the pleural cavity, one had a fairly large extrapleural hematoma, and one had free air in the mediastinum but no evidence of extravasated blood in the chest. In only two cases

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TABLE I. HEMODYNAMIC DATA ON THIRTEEN PATIENTS WITH CHEST INJURIES

PATIENT	DIAGNOSIS	AGE	SEX	SURFACE AREA	OXYGEN CONSUMPTION	VENTILATION	ARTERIAL OXYGEN CONTENT	MIXED VENOUS OXYGEN CONTENT	ARTERIOVENOUS OXYGEN DIFFERENCE	CARDIAC INDEX	HEMOGLOBIN	HEMATOCRIT READING	FEMORAL ARTERIAL PRESSURE			PULSE RATE	PERIPHERAL RESISTANCE	ATRIAL PRESSURE	BLOOD VOLUME	OXYGEN SATURATION OF ARTERIAL BLOOD	BLOOD ALCOHOL‖
													SYSTOLIC	DIASTOLIC	MEAN						
		YRS.		SQ. M.	C.C. PER MIN. PER SQ. M.	L. PER MIN. PER SQ. M.	VOLUME PER CENT			L. PER MIN. PER SQ. M.	GM. PER 100 C.C.		MM. HG			BEATS PER MIN.	ABSOLUTE UNITS	MM. H_2O	C.C. PER SQ. M.	PER CENT	MG. PER 100 C.C.
J. McM.	Hemothorax, transsection of cord, bullet wound	23	M	2.04	160	4.3	15.7	9.5	6.2	2.5	12.7	43	36	26	32	100	490	65		89	88
W. W.	Hemothorax, stab wound	33	M	1.83	192	4.7	16.2	10.6	5.6	3.4	14.9	43	63	45	51	75	650	45	3,170		52
W. L. T.	Extrapleural hematoma, stab wound	52	M	1.87	107§	3.5	13.6	9.4	4.2	2.6	10.0	32	71	42	50	75	830	25	2,660		290
P. D.	Hemothorax, stab wound	34	M	1.67	151	3.3	15.0	10.1	4.9	3.3	8.2	27	80	48	62	65	1,030	5	1,780		
O. M.	Hemothorax, stab wound	20	F	1.46	122	3.8	9.4	5.7	3.7	4.4	12.5	42	88	56	66	88	730	20			155
L. D.	Hemothorax, stab wound	27	M	1.65	167	3.8	14.7	10.9	3.8	3.3	10.0	31	92	53	69	125	920	25	2,360	92	
T. L.	Hemothorax, bullet wound	28	F	1.83	160	3.8	12.2	7.3	4.9	4.0	11.9	37	94	59	68	92	840	35			121
J. B. R.	Hemothorax, stab wound	42	M	1.61	158	3.3	15.2	11.3	3.9	3.1	13.5	39.5	77	46	54	77	850	65	2,980	88	90
A. E.*	Hemothorax, fractured ribs	71	F	1.57	104	6.4	8.2	2.6	5.6	1.8	8.6	29	105	45	54	103	1,250	70	1,710	67	
D. S.	Hemothorax, stab wound	35	F	1.69	130	2.8	14.4	10.9	3.5	3.8	9.6	38	103	67	83	111	738	85	2,030		
R. G.	Hemothorax, stab wound	44	M	2.0	149	4.9	15.5	11.7	3.8	3.9	13.3	40	119	77	93	94	940	100			
J. T. C.	Hemothorax, stab wound	31	M	1.6	207	4.8	16.6	11.9	4.6	4.5	13.7	44	139	80	103	94	1,140	40		91	63
M. M.	Mediastinal emphysema, stab wound	40	M	1.74	189	4.5	10.7	7.1	3.6	5.0	13.6	42	154	86	104	125	1,320	0			95
Averages of the four patients without clinical evidence of circulatory insufficiency					169	4.2			3.9	4.3		41	129	78	96	106	1,040	56			
Averages of the eight patients with clinical evidence of circulatory insufficiency					152	3.8			4.7	3.3		37	75	47	57	87	790	36	2,600		
Averages of 13 patients with acute hemorrhage†					128	4.0			5.5	2.6		33	86	54	65	96	1,330	2	2,100		
Average normal values‡					128	3.4			4.0	3.3			124	67	85	68	1,160	31			

*Not included in averages. †Reference 1. ‡Reference 2. §Air sample taken after albumin was given. ‖The blood alcohol determination was made if there was the clinical evidence

was there evidence of free air in the pleural cavity, and this was only slight. Only one patient (A. E.) was cyanotic.

Four of the patients with penetrating pleural wounds showed no clinical evidence of circulatory insufficiency on admission to the hospital. The data on the circulation in these patients were similar to those obtained in apprehensive normal subjects.[2] The cardiac output was somewhat elevated and the heart rate was increased. The atrial pressure was unaltered.

In nine patients clinical evidence of circulatory insufficiency was present. Eight of these patients were observed shortly after injury. One of them, J. McM., had, as a complication, a transverse section of the dorsal cord. The ninth was a 71-year-old woman (A. E.), who had fractured several ribs and the tibia twelve hours before admission. Because none of our normal subjects were elderly, the data of patient A. E. were not averaged with those of the other eight patients with circulatory insufficiency from chest wounds. In each of the other eight patients with clinical signs of circulatory insufficiency the systolic arterial pressure was below 100 mm. Hg; in five it was 80 mm. or lower. In general, the pulse rate was not greatly elevated. In three it was 75 beats per minute or lower. The atrial pressure was not significantly different from that found in normal subjects.

The cardiac output was surprisingly high in these eight patients with signs of circulatory insufficiency. The marked fall in arterial pressure without a corresponding fall in cardiac output indicated a decrease in peripheral resistance. This could not be correlated with the level of the blood alcohol. In only three instances was the cardiac index below the average normal value of 3.3, and even in these patients it was not below the lower range of normal values.[2] In general the values were similar to those found in normal subjects in the basal state. As these patients were not basal and were generally in some pain it may be argued that the finding of a cardiac index comparable to that present in the normal basal state indicated some degree of circulatory insufficiency. The fact that the arteriovenous oxygen difference was only slightly increased above normal argues against any considerable degree of disproportion between the requirements of the body for blood and the cardiac output.

The oxygen consumption tended to be somewhat elevated. The plasma volume was measured in five of the eight subjects and found to be diminished from hemorrhage in three of them. The average ventilation in the eight patients with circulatory insufficiency was found to be 3.8 liters per minute per square meter. In the four patients who were not in circulatory difficulty the average ventilation was 4.2 liters per minute per square meter. This compares with a value of 3.4 for normal subjects and 4.2 for patients with moderate chronic anemia.[3]

Five patients received 50 Gm. of human albumin* intravenously. The arterial pressure rose during the therapy. The average increase in cardiac index was 0.9.[4] The therapy may or may not have caused improvement. Spon-

*The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

taneous recovery may have occurred. Five patients with hemorrhage from superficial lacerations were treated with albumin and the average rise in cardiac index was 1.8.[4]

DISCUSSION

The clinical picture of these patients with penetrating wounds of the pleura is similar to that presented by patients with acute blood loss from multiple lacerations. The hemodynamic data, however, differ in several important ways in the two groups. Patients with simple acute blood loss and a systolic arterial pressure below 100 mm. Hg usually have a diminished cardiac output, a low atrial pressure and an elevated peripheral resistance. When the blood volume is increased by therapy, the rise in cardiac output is marked. In the patients reported here with knife wounds of the pleura, the cardiac output was relatively normal in spite of the sharp fall in arterial pressure and did not increase markedly when the blood volume was raised. The atrial pressure was not decreased and the peripheral resistance was lowered. It seems therefore that the sequence of events leading to the fall in arterial pressure is not the same in patients with chest wounds as in patients with blood loss alone.

The sudden circulatory collapse which occurs in donors while blood is being removed has been studied in this[5] and other laboratories.[6, 7] The subjects become pale, sweat profusely, and complain of nausea and weakness. The heart rate slows, the atrial pressure remains unchanged or increases, and the cardiac output remains unchanged. There is a striking fall in arterial pressure and peripheral resistance. The circulatory collapse appears to be the result of a sudden decrease in peripheral resistance because of vasodilatation, presumably in the arterioles. As this type of circulatory collapse does not result from a marked fall in atrial pressure and as it may occur before any blood is actually withdrawn, the fall in arterial pressure and peripheral resistance is believed to result from reflex dilatation of the arterioles. The skin vessels are contracted as shown by the marked pallor, but the vessels in the muscles are dilated.[6] It is not unusual for the vessels supplying the skin and muscles to react in an opposite way to the same stimulus.[8] The afferent impulse initiating the vasodepressor reflex may come from any of the special sense organs or any sensory nerves.

The changes in the circulation noted in these patients with circulatory collapse from chest wounds are similar to the changes found in subjects with acute reflex arteriolar dilatation. The afferent impulses for the vasodepressor reflex may well originate in the pleura. It has been shown in dogs that irritation of the pleura will result in a striking fall in arterial pressure.[9] In the patients reported here extensive trauma to the chest wall was not present and all of the wounds were easily closed. The findings in patients with crushing wounds of the thorax and with extensive destruction of the chest may differ from those in our patients.

SUMMARY AND CONCLUSIONS

1. Quantitative hemodynamic data on 13 patients with chest injuries are presented. Four of these patients had no evidence of circulatory difficulties

while nine of them did. The studies on those without circulatory difficulty gave values which were similar to those on normal subjects previously reported from this laboratory.

2. The nine patients who had circulatory insufficiency showed hypotension, a low peripheral resistance, a relatively normal cardiac output, and a normal right atrial pressure. A group of patients who had circulatory insufficiency following acute hemorrhage showed hypotension, an increased peripheral resistance, a low cardiac output, and a low right atrial pressure.

3. The circulatory failure in these patients with penetrating wounds of the pleura appeared to be primarily the result of arteriolar dilatation. It is believed that the arteriolar dilatation is reflex in origin and it is suggested that the afferent impulses may arise in the pleura.

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PERICARDIAL TAMPONADE FROM STAB WOUND OF THE HEART AND PERICARDIAL EFFUSION OR EMPYEMA: A STUDY UTILIZING THE METHOD OF RIGHT HEART CATHETERIZATION

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PATIENTS with penetrating wounds of the heart with pericardial tamponade often present the clinical picture of profound shock. Study of these patients demonstrates the presence of a significantly different hemodynamic situation from that occurring in patients with shock produced by hemorrhage or by stab wounds of the chest. Observations on the changes in the circulation in seven patients with pericardial tamponade from stab wounds of the heart or from infection of the pericardium form the basis for this report.

METHODS

The methods used in this study have been described previously.[1, 2] The technique of right atrial catheterization was utilized for obtaining samples of mixed venous blood and for measuring the atrial pressure. The cardiac output was calculated utilizing the Fick principle. The arterial pressure was recorded optically from a needle placed in the femoral artery.

A comparison of the output of the heart per minute between subjects of different size is of little value. The heart of a large person normally pumps more blood than that of a small person. For this reason the cardiac index which is the output of the heart per minute per square meter of body surface is used in comparing the observations on patients with pericardial tamponade with those made on other groups.

RESULTS

Four patients with stab wounds over the precordium were studied soon after injury. Three of the four had a low arterial pressure and were sweating profusely on admission. S. W. was in shock when the first observations were obtained. R. B. received 1,000 c.c. of physiologic saline solution and 500 c.c. of blood in the emergency clinic and showed no sign of shock by the time the catheter was passed. W. S. was pulseless on admission but had improved without treatment before studies were made. All had evidence of increased venous pressure on inspection of the neck veins. On fluoroscopy the excursions of the heart borders were either not visible or greatly diminished. In one (S. W.), pericardial tamponade was proved at operation. In the other three the location

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of the stab wound, the decreased pulsations of the borders of the heart, the increased atrial pressure, and the paradoxical pulse made the clinical diagnosis fairly definite.

The cardiac output was definitely decreased in S. W. and probably decreased in W. S. These patients were not basal, were somewhat apprehensive, and would have been expected to have had a cardiac index at least as high as the average normal value (3.3) found in basal subjects.[2]

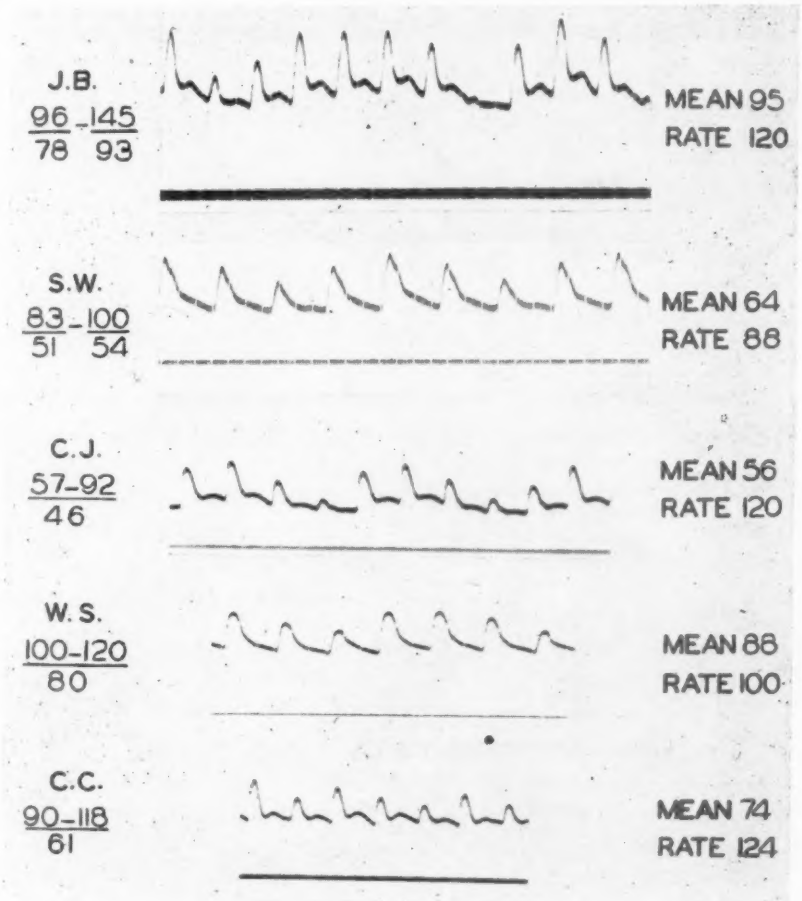

Fig. 1.—Femoral arterial pressure tracings showing paradoxical pulse of patients with pericardial tamponade, two as result of hemopericardium from stab wounds and three as result of pericardial infection.

The atrial pressure was greatly elevated in all the patients. There was no correlation between the height of the atrial pressure and the cardiac output. The arterial pulse was paradoxical (Fig. 1) in every instance. The systolic pressure fell 16 to 20 mm. Hg even during quiet inspiration. The peripheral resistance was in the high normal range in the two instances in which the cardiac output was decreased. The pulse rate ranged from 76 to 100 beats per minute and was 88 in the patient with the lowest cardiac index.

TABLE I. HEMODYNAMIC DATA OF SEVEN PATIENTS WITH PERICARDIAL TAMPONADE

PATIENT	DIAGNOSIS	AGE	SEX	SURFACE AREA	ORAL TEMPERATURE	OXYGEN CONSUMPTION	ARTERIAL OXYGEN CONTENT	MIXED VENOUS OXYGEN CONTENT	ARTERIOVENOUS OXYGEN DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	HEMOGLOBIN	HEMATOCRIT	RESPIRATION VARIATION IN SYSTOLIC BLOOD PRESSURE	MEAN	PULSE RATE	ATRIAL PRESSURE	PERIPHERAL RESISTANCE	BLOOD ALCOHOL
		YRS.		SQ. M.	° F.	C.C. PER MIN. PER SQ. M.	VOLUMES PER CENT			L. PER MIN.	L. PER MIN. PER SQ. M.	GM. PER 100 C.C.	PER CENT	MM. OF HG		BEATS PER MIN.	MM. H_2O	ABSOLUTE UNITS	MG. PER 100 C.C.
S. W.	Stabbed heart	32	M	1.8		111	16.2	10.4	5.8	3.4	1.9	–	45	17	64	88	160	1,500	230
	After 50 Gm. of albumin intravenously					109	14.1	9.4	4.7	4.2	2.3	15.4	39	12	73	84	255	1,390	
W. S.	Stabbed heart	19	M	1.86		139	13.9	7.7	6.2	4.2	2.3	12.7	41	20	88	100	180	1,680	147
	17 days later					161	15.1	10.7	4.4	6.8	3.7	12.5	40	0	112	65	60	1,320	
N. B.	Stabbed heart	39	M	1.72		180	12.8	7.0	5.8	5.4	3.2	11.0	34	16	72	88	135	1,070	360
	After 500 c.c. 5% albumin					179	11.7	6.9	4.8	6.6	3.8	10.7	32	12	77	88	190	930	
R. B.*	Stabbed heart	42	M	1.76		199	14.3	9.1	5.2	7.0	4.0	13.0	40	17	89	76	240	1,020	
	4 days later					143	16.5	12.2	4.3	5.9	3.4	13.5	43	5	102	97	- 5	1,380	
C. J.	Amebic pericarditis	17	M	1.55	97.4	127	10.4	2.0	8.4	2.3	1.5	8.3	28.4	35	56	120	300	1,960	
	7 minutes after withdrawing 720 c.c. of fluid					155	10.6	6.1	4.5	5.3	3.4	8.5	28.8	12	79	104	180	1,200	
C. C.	Anaerobic streptococcus pericarditis 15 minutes after withdrawing 410 c.c. of fluid		M	1.82	102.4	275	15.8	7.8	8.0	6.3	3.5	13.8	44	28	74	124	195	940	
						243	12.7	8.5	4.2	10.5	5.8	13.4	43	14	92	112	125	700	
J. B.	Tuberculous pericarditis	62	M	1.90	100.4	166	12.3	5.7	6.6	5.0	2.6	10.1	33	49	95	120	190	1,530	
	After withdrawing 1,100 c.c. of fluid					178	12.8	7.9	4.9	6.9	3.6	10.1	31	23	92	124	90	1,070	

*Five hundred cubic centimeters of blood and 1,000 c.c. of physiologic saline were given prior to control studies.

Two patients were given fluid intravenously after the initial observations had been made. N. B. received 25 Gm. of albumin* in 500 c.c. of physiologic saline solution, and S. W. received 50 Gm. of albumin in 200 c.c. of fluid. The atrial pressure rose 55 and 95 mm. of water, respectively. In each instance the arteriovenous oxygen difference decreased, the cardiac output rose, the mean arterial pressure increased, and the femoral pulse became somewhat less paradoxical. The evidence of an improved circulation was not striking but because the changes in blood pressure, arteriovenous oxygen difference, and cardiac output all went in the same direction, it was believed that the therapy with albumin was beneficial.

Three patients with pericardial tamponade as a result of infection of the pericardium were studied. All had distended neck veins and paradoxical pulse, but only one of these had marked clinical evidence of shock.

The cardiac output was inadequate for the needs of the body in each instance, as shown by the elevated arteriovenous oxygen difference before therapy and by the sharp rise in output as the tamponade was relieved. In two patients the absolute values for the cardiac index were low and the values for the peripheral resistance were in the high normal range. In all three of the patients a rise in output and a fall in peripheral resistance occurred as the pericardial fluid was removed. The arterial pulse was markedly paradoxical in each instance falling from 28 to 49 mm. Hg during quiet inspiration. The atrial pressure varied from 190 to 300 mm. of water (average normal value, 31 mm. of water).[2] The pulse rate was uniformly elevated.

The pericardial sac was tapped and from 410 to 1,100 c.c. of fluid were removed. The arteriovenous oxygen difference decreased, the cardiac output increased, the pulse became less paradoxical, and the peripheral resistance decreased. The fall in atrial pressure ranged from 70 to 120 mm. of water. The condition of the patients was improved greatly.

DISCUSSION

The clinical picture of pericardial tamponade has been well described. Its occurrence from a stab wound of the heart is not uncommon at Grady Hospital.[3] On admission the patient is confused, pulseless, and frequently incontinent of urine and feces. The veins of the neck are distended, and the pulse if palpable is paradoxical. The patient may remain in this condition, he may spontaneously improve, or he may improve while fluids are being administered intravenously. The pulsations of the cardiac borders are either diminished or absent. This finding and the increased venous pressure persist even if the circulation improves.

When the patient is first seen it is difficult to be certain whether circulatory failure is the result of reflex arteriolar dilatation as frequently occurs in stab wounds of the chest[4] or whether it is the result of pericardial tamponade. In certain patients with prompt improvement of the circulation without therapy,

*The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

reflex vasodilatation is the most likely primary cause of the shock picture. In others the persistence of the circulatory failure until the pressure within the pericardial sac is lowered is proof that the tamponade is the primary cause of the circulatory failure. External hemorrhage can be excluded as the primary factor because of the increased atrial pressure, but even then blood loss may be a contributory factor. Increased atrial pressure and paradoxical pulse are the first signs of circulatory failure produced by the rise of pressure within the pericardial sac. The pulse may become distinctly paradoxical before there is a detectable reduction in the minute output of the heart.

It is of interest to note that the atrial pressure in the two patients with decreased cardiac output did not rise over 180 mm. of water. In a third patient, not included in the table because the patient died before the cardiac output could be measured, the atrial pressure was 180 mm. of water. R. B. had a very high atrial pressure with a normal cardiac output. He had received 500 c.c. of blood and 1,000 c.c. of physiologic saline solution before the atrial pressure was measured. The rise in venous pressure in the untreated patient with acute pericardial tamponade results from a redistribution of blood within the vascular tree and from vasoconstriction.[5] A small amount of blood may be shifted from the arterial to the venous system as the arterial pressure falls, and blood within the venous system may be redistributed by constriction of the smaller vessels so that the pressure in the venous system rises. The height to which the venous pressure rises will be determined by the ability of the veins to constrict and by the quantity of blood in the vascular bed. The factors causing the venous constriction have not yet been determined.

If the blood volume is reduced by hemorrhage the venous pressure rise will be lessened. In patients with chronic congestive failure the rise in venous pressure results in part from the increase in blood volume.[5] Because the blood volume is usually somewhat decreased by hemorrhage and is never increased in patients with stab wounds of the heart, the venous pressure in these patients with sudden tamponade usually does not reach the extreme heights to which it may rise in chronic congestive heart failure.

If the blood volume is raised by giving blood or other fluids intravenously the venous pressure can be increased above the level present before treatment. The high atrial pressure in R. B. was probably the result of the blood and saline solution which he received prior to our studies. The question has been asked as to whether raising an already elevated venous pressure by giving of fluids intravenously will benefit the circulation in patients with stab wounds of the heart. The problem has been approached experimentally in two laboratories. In one[6] a further rise in venous pressure was found to be beneficial; in the other[7] no improvement was observed. It is clear that a rise in venous pressure will not improve the circulation unless the heart is able to receive more blood during diastole. This will be possible only if the increased atrial and pericardial pressures either cause the pericardium to stretch or force some of the blood out of the pericardial sac. The results of administering fluids intravenously in the clinic led us to believe that a further rise in venous pressure was beneficial.

Quantitative studies in two patients showed some but not a striking improvement when the atrial pressure was raised above the level present on admission by the use of human albumin solution (Fig. 2).

The relation between the cardiac output and the arterial pressure in the four patients with low cardiac indices (two with stab wounds of the heart and two with pericardial effusion) showed no evidence of arteriolar dilatation. The peripheral resistance was in the high normal range in all of these patients. This high peripheral resistance is similar to that seen in patients with circulatory failure from acute hemorrhage[1] and is in sharp contrast to the low peripheral resistance seen in patients with circulatory failure from reflex stimulation of the pleura from a penetrating wound of the chest.[4] A rise in peripheral resistance with a falling cardiac output is also characteristic of congestive heart failure.[8]

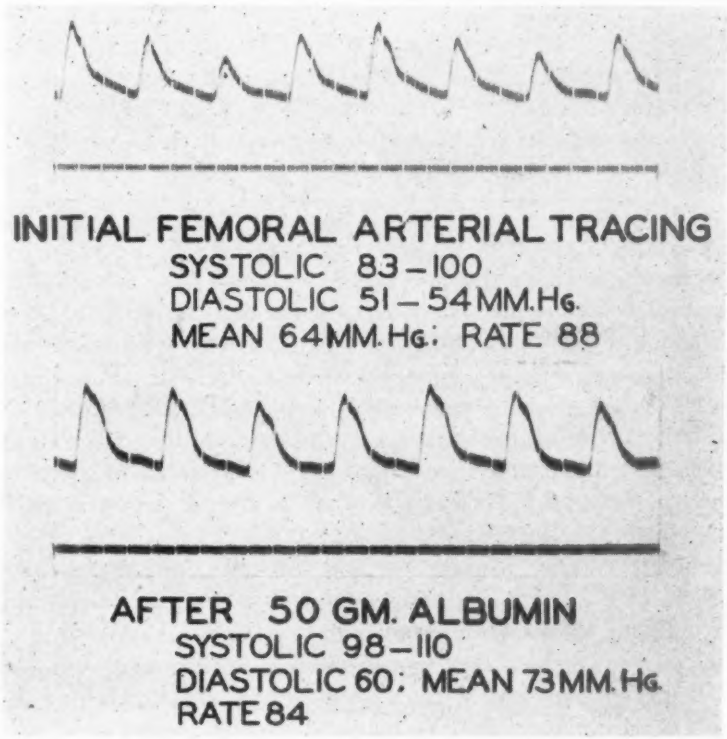

Fig. 2.—Femoral arterial pressure tracings of patient S. W. who had pericardial tamponade as result of a stab wound of the heart.

The patients with massive pericardial effusions were severely ill. They showed the same disturbances in the circulation which were found in the patients with tamponade from stab wound of the heart. In the two patients with the greatest decrease in cardiac output, the peripheral resistance was in the high normal range. The atrial pressure fell very slowly during aspiration of the pericardial sac, remaining above normal after as much as 1,100 c.c. of fluid were removed. The reason for this slow fall in pressure was not established. It is

possible that the pericardial pressure was still elevated sufficiently to account for the high atrial pressure. These patients had been in circulatory failure for some time and a rise in blood volume may have occurred as happens in persons with prolonged circulatory insufficiency from heart failure.[5]

Since aspirating the pericardium produces such dramatic improvement in patients with pericardial tamponade from large effusions, it seemed logical to attempt this procedure in patients with tamponade from a stab wound in the heart. In one of the patients reported here and in two not reported because complete data were not obtained, aspiration was not successful. At operation or autopsy the blood in the pericardium in these three patients was found to be clotted. In two patients not included in this report aspiration was successful. In both of these the aspiration was done immediately after the patient entered the hospital without waiting for detailed studies on the circulation.

The following routine has now been established in the emergency clinic at Grady Hospital. The patient is given an infusion of saline solution and is fluoroscoped immediately. If he has the clinical and x-ray signs of pericardial tamponade, aspiration is attempted at once. The patient receives a transfusion and the operating room is set up. If the aspiration is unsuccessful or if the signs of pericardial tamponade recur after a successful aspiration, the heart is sutured.

SUMMARY AND CONCLUSIONS

1. The disturbances in the circulation produced by pericardial tamponade have been studied by the method of right heart catheterization. Four patients had stab wounds of the heart and three had pericardial effusion or empyema.

2. The circulatory failure observed in patients with stab wounds of the heart may be caused either by pericardial tamponade, by reflex arteriolar dilatation, or by both. Tamponade causes a decrease in cardiac output and a fall in arterial pressure without arteriolar dilatation. The relation between the cardiac output and the arterial pressure is similar to that observed in patients with circulatory failure from acute hemorrhage.

3. Paradoxical pulse, elevated venous pressure, and decreased pulsation of the borders of the heart on fluoroscopic examination may occur before other signs of circulatory failure are present.

4. The height to which the venous pressure rises in acute pericardial tamponade depends on the size of the blood volume and the degree of venoconstriction. Therefore, there will be no rigid correlation between the degree of circulatory failure and the height of the venous pressure.

5. Raising the venous pressure by increasing the blood volume through the rapid intravenous infusion of human albumin solution appeared to cause some improvement in the two patients in whom quantitative data were collected. This is in agreement with our clinical impression from observing the results of treating a larger group of patients in whom quantitative data were not obtained.

6. Aspiration of the pericardium is a satisfactory method of relieving pericardial tamponade in certain patients with stab wounds of the heart. It

should be performed as quickly as possible because the blood in the pericardium will clot.

7. The changes in the circulation in patients with tamponade from empyema or chronic effusion of the pericardium are similar to those observed after stab wounds of the heart. The atrial pressure fell slowly as the pericardial fluid was removed and in one instance remained elevated after 1,100 c.c. of fluid were removed.

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THE EFFECTS OF MALARIA ON THE HEART

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ALTHOUGH it is probably true that malaria is the most widespread and serious disease in the world, this knowledge had not had a proportionate influence upon medical thinking in the United States until our experience in the Pacific during World War II brought the problem to the fore. Of the so-called tropical diseases brought back to us from the combat areas, malaria is the one about which there arise the most frequent questions. There is concern not only about the public health aspects of malaria, but also about its permanent effects upon individuals infected with the plasmodia.

Though malaria is a disease from which no organ or tissue is exempt, this paper is concerned with its influence upon the circulation, and more particularly upon the heart itself. Of the characteristics peculiar to malaria, those which might be expected to affect the heart are (1) its chronic and recurrent nature, (2) the systemic toxemia of the paroxysm, (3) the profound anemia produced by hemolysis and suppression of hemopoiesis, and (4) the occlusion of capillaries and arterioles of the myocardium. The published clinical and pathologic studies of malaria indicate that these are, in fact, the mechanisms involved.

REVIEW OF LITERATURE

Medical literature, especially that from France, Italy, and Latin America, abounds with references to a great number of cardiovascular injuries attributed to malaria. While in general these references seem to be a mass of supposititious material, it must be conceded that the implications in these papers are partly based on observations of long-standing, inadequately treated cases which would not be seen in our Army, Navy, and Marine Corps personnel.

Long before the malarial parasite was discovered in 1880, it was believed that the heart was frequently injured by the disease.[1] Laveran published a description of such cases, and in 1890 they were summarized by Ranzier. Duroziez reported instances in which malaria had produced various valvular and myocardial changes in which pigmentation was prominent. Tremolières and Caussade described aortic, coronary, endocardial, mural, and arterial injuries in acute and chronic cases of malaria. They found 42 cases of patients with cardiac involvement among 1,000 patients with malaria. In 17 of these 42 cases, the involvement was functional: four had precordial pain; four, palpitation; three, breathlessness; and five, permanent, and one, paroxysmal, tachycardia. Castellani reported a case of heart block in a middle-aged man cured by the use

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of quinine and three cases of angina pectoris cured by the same drug. Lanceraux quotes the case of a woman 34 years of age with angina pectoris and a double aortic murmur which he believed were due to malarial aortitis.

It is of interest to remember that the "de Musset sign," nodding of the head with each heart beat when there is pronounced aortic regurgitation, was named for Alfred de Musset by his brother, who ascribed his aortitis to malaria acquired in Italy.

Recent writers have described electrocardiographic changes in malaria, including right bundle branch block (old terminology) and T-wave changes.[2, 3]

EFFECTS OF MALARIA ON THE CIRCULATION

Clinical Aspects.—The effect of malaria on the circulation differs with the stage and severity of the disease. In malarial damage to the brain, it has been our experience that functional cerebral disturbances most often occur and true "cerebral malaria" in which thrombosis of the brain capillaries is the characteristic pathology occurs but rarely. So in cardiac malaria a series of functional aberrations may be commonly found, but the syndrome of heart failure is very infrequent. Gaskell and Millar, in a review of their experience in World War I[4] with very severe cases of malaria in Serbians, divided the fatal cases into the true cerebral, the septicemic, and the cardiac types. They stated that, "The cardiac type is only likely to be fatal when hospital arrangements have to cope with an overwhelming number of serious cases."

It was shown by Brown and Loevenhart (1913)[5] that the injection of alkaline hematin into dogs and cats caused dilatation of the splanchnic vessels, constriction of cutaneous vessels, and marked fall in blood pressure. The slowing of the heart and reduction in cardiac output are due mainly to the toxic effect on the vasomotor and cardioinhibitory centers.

Meleney[5] states that serious circulatory disturbances in man occur almost entirely in falciparum infection. Before the paroxysm there are a vagal bradycardia, lowered blood pressure, and slight miosis.[12] During the cold stage there is an increasing sympathetic effect, with a return to vagotonia during the sweating stage. Tachycardia and premature beats may be manifestations of a direct toxic effect of malaria on the myocardium, and may persist in the chronic phases of the disease. Manson-Bahr, in 1920, said, "The most acute cases die of heart failure, apparently a toxaemic myocarditis."[6]

Pathologic Findings.—Pathologic studies of the heart in fatal malaria have been extensive. Over 40 years ago Ewing[7] described the dilated, pale, or slightly brownish-tinged heart muscle with perinuclear masses of greenish pigment in the cells. In one exceptional case the distended capillaries of the heart wall were filled with young parasites and pigmented cells. In 1917 at Salonica Dudgeon and Clarke[8] found myocardial changes in malaria similar to those of diphtheritic myocarditis. Of their 45 fatal cases, 23 showed fatty degeneration of the heart muscle. There was also blocking of the capillaries and arterioles, local hemorrhage, and deposit of pigment. Fragmentation of the muscle may be extreme. Gaskell and Millar found the subtertian parasites among or

within the cardiac muscle cells. In chronic cases there may be fatty degeneration especially of the muscle of the left ventricle. This has even resulted in cardiac aneurysm or rupture of the ventricle.[6] Gallenga[9] described primary degenerative changes in the cardiac nerves in a case of angina pectoris of malignant tertian origin. Anderson[1] believes that malaria has two cardiac effects, that on the extrinsic vagosympathetic nerves and a direct intracardiac neuritis. Seyfarth,[6] in his detailed paper on the pathologic anatomy of malaria, found that cardiac deaths comprised about 14 per cent of the malarial fatalities; septicemic deaths, 30 per cent; cerebral deaths, 55 per cent; and renal deaths, 1 per cent. He described the pathology of the cardiac type as consisting of blockage of the coronary radicles with parasites and pigment, and either a toxic myocarditis or heart muscle necrosis, or fatty change with especial involvement of the conduction system.

In describing the effects of malaria on the peripheral vascular system, the older writers describe malarial arteriosclerosis, obliterative endarteritis, venous thrombosis, and the previously mentioned "aortite paludéene."

Contemporary authors generally agree, however, with the recent statement of Cannon[10] that the reticulo-endothelial system is most commonly affected in malaria, and that the myocardium and other organs are rarely affected. Endothelial phagocytosis fortunately occurs mainly, if not wholly, in the spleen, liver, and bone marrow. Furthermore, it must be emphasized that the malignant tertian (falciparum) malaria parasite is the predominating organism in fulminating, vascular occlusive, fatal malaria regardless of the type of terminal process.

EXPERIENCE WITH SOUTH PACIFIC MALARIA

The author served as Chief of Medicine in a Naval Mobile Hospital in New Zealand for a year between Aug. 7, 1942, when the Marines started the Solomon Islands Campaign, and August, 1943, when he joined a hospital ship in the South Pacific Area. Since January, 1944, he has been Chief of Medicine in a large continental Naval hospital. These posts have permitted observation of malarial patients from the early days of their infection to a time almost three years later, when the men with relapses are still being admitted to the hospital. Although many thousands of patients with malaria have passed through these medical services, there has been no clear-cut case of malarial heart disease. The most severe cases of malaria, of course, were seen in New Zealand in Marines from Guadalcanal. At this time prophylaxis, therapy, and malaria control were not well understood.[11] Although three patients died from malaria with cerebral manifestations, there was no specific pathology in the heart at autopsy. The only patient showing clinical cardiac effect was one who, during intravenous quinine therapy, developed probable complete A-V block with ventricular fibrillation. The electrocardiogram taken after the patient had responded to intravenous adrenalin showed auricular paroxysmal tachycardia with right axis deviation. The patient made a complete cardiac recovery.

Patients with many relapses of vivax malaria continue to enter Naval hospitals in the United States. We have observed approximately 2,000 relapse ad-

mission cases in the past sixteen months. In none of these patients with chronic relapsing malaria was any cardiac condition discovered which could be specifically attributed to malaria. Any chronic disease, especially one resulting in anemia, may produce the symptoms of irritable heart with tachycardia and premature beats. Functional systolic murmurs may be found but even these have not been common among the patients at the hospital.

A series of 50 cases of recurrent malaria, all but one of the vivax type, were studied electrocardiographically.* All of the patients had had recurrent malarial attacks, some over a period of thirty-three months. Two had cerebral symptoms indicating a probable organic change caused by vascular occlusion and resulting in the malarial encephalopathy syndrome. The electrocardiograms were often recorded directly after the chill, while the patient was still febrile. Some of the patients had had over a dozen relapses. One patient, in addition to eleven recurrences, had had scrub typhus and scarlet fever, but the cardiac findings were normal. In two typical patients observed directly after the chill the electrocardiograms were normal, and the pulse rates were 76 and 78. The one patient with falciparum parasites in the blood had acquired the infection three months before on the west African coast. Again there were no cardiac abnormalities.

Among the entire group of 50 patients there was no electrocardiographic finding which could not be considered either within normal variants or of nonspecific import. In tracings of malarial patients studied in the various Naval activities mentioned, we have recorded ventricular and auricular premature beats, low T waves associated with anemia, nodal tachycardia, right axis deviation of slight degree, sinus bradycardia and tachycardia, and a P-R interval of 0.21 second.

DISCUSSION

From the evidence presented in the literature it seems justifiable to consider that malaria, especially of the malignant tertian type, may rarely be fatal by its direct myocardial effect, which is either toxic or anoxic through coronary capillary occlusion. On the other hand, even when malarial patients die from septicemic or cerebral mechanisms, the heart seems to be very infrequently affected.

There is also evidence in the literature that prolonged relapsing malaria in natives of malarious countries may result in chronic cardiac disturbances, which may progress even to the point of cardiac dilatation, ventricular aneurysm, and cardiac rupture. In chronic malaria the influence of malarial cachexia, which is a complex nutritional and hemoclastic affair, accompanied by widespread pigment deposit throughout the body and by capillary occlusion, may produce changes in the circulation indistinguishable from those of chronic anemia. There is no evidence of critical value to show that valvular heart disease or aortitis results from malaria.

The possibility that members of our own Armed Services may develop cardiac pathology from recurrent malaria is very remote. Our men are treated

*This was done with the cooperation of Commander William A. Coates, M.C., USNR, in charge of the malaria service.

early and adequately; the factors of malnutrition, avitaminosis, anemia, and complications (such as blackwater fever) are vigorously attacked, and hospitalization is readily available.

CONCLUSIONS

According to the literature heavy plasmodial infection (especially with *Plasmodium falciparum*), or untreated or inadequately treated malaria can cause death from myocardial inflammation or capillary infarction, and chronic recurrent malaria can produce myocardial pathology similar to that caused by prolonged anemia. However, malaria, in our experience with several thousand cases occurring in members of the Armed Forces of the United States, has resulted neither in acute cardiac death nor in any proved chronic cardiac disease.

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FURTHER OBSERVATIONS ON THE USE OF MERCUPURIN ADMINISTERED ORALLY

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SINCE the presentation of the original report[1] on the oral use of Mercupurin, additional information concerning its value for the treatment of congestive heart failure has become available. It must be stressed that the oral administration of a mercurial diuretic is not recommended to replace the intravenous preparations. We are not concerned with the comparative potency of the oral and parenteral preparations in the same patient, for there is no doubt that the intravenous preparations are superior to oral preparations and are more reliable in producing a diuresis. However, many patients can be benefited by the oral use of a mercurial. This investigation was, therefore, undertaken in an effort to answer the following two questions: (1) Is the mercurial diuretic in the form administered orally an effective and safe diuretic for relieving the signs and symptoms of congestive heart failure present in the average patient? (2) If the oral preparation is effective, how should it be administered in order to obtain its maximum value? Factors such as degree of edema, severity of the heart disease, the effect of the concomitant administration of other medications, and the question of whether the patient is ambulatory or bedridden must be carefully considered.

The oral preparation of Mercupurin* was studied in both hospitalized and ambulatory patients, according to several plans. Although the single and multiple dose methods of administration have already been reported, for the sake of completeness, summaries of our experiences with all methods of administration have been included in this report. A total of 81 patients presenting all stages of congestive heart failure were given Mercupurin orally. Fifty-six were treated exclusively as hospitalized patients, five were observed as both hospitalized and ambulatory patients, and 20 were treated solely as ambulatory patients.

The method for studying diuretics which has proved most satisfactory in our hands has been presented previously.[2-4] A practical and relatively quick appraisal of the effectiveness of a diuretic can be gained in hospitalized patients by administration of the preparation after a preliminary period sufficiently long to evaluate concomitant therapeutic measures, such as bed rest, digitalization,

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*Each tablet contains 120 mg. of Mercupurin, which is equivalent to 30 mg. of mercury and 27 mg. of anhydrous theophylline, whereas 1 c.c. of the parenteral solution contains 135 mg. of Mercupurin. Mercupurin tablets were supplied by Campbell Products, Inc., New York, N. Y.

or the effectiveness of other diuretic agents. The length of this control period depends upon the condition of the patient and may vary between three days and several weeks. As a rule, when a patient is hospitalized for severe congestive heart failure, he is watched constantly for any change in clinical status. If he becomes worse he is given the diuretic immediately. The majority of patients, however, are observed for several days in order to exclude the spontaneous diuresis which so often occurs after a few days of bed rest. Patients who respond to digitalization are not given the diuretic. If digitalis alone no longer produces satisfactory diuresis, the mercurial is administered after the maintenance dose of digitalis has been established. If improvement is evidenced by the weight curve, it can be assumed, especially if consistent results are obtained in a majority of the patients, that the diuretic was responsible for the improvement. A diuretic response is considered to be an effective one if the patient loses at least three pounds of edema fluid. In the single dose method, this response should occur within forty-eight hours. When the multiple dose method is used, the diuresis should occur during the period of administration, or at least no later than twenty-four hours after the drug is discontinued.

I. Single Dose Method.—In an effort to determine whether or not Mercupurin administered orally in a single dose could produce an effective diuresis, five tablets (a single dose) were given to 24 patients, some of whom were treated more than once, for a total of 31 trials. A satisfactory response was obtained in 18 trials (58 per cent), or 16 patients (67 per cent). Diuresis usually began within four to twelve hours, and with few exceptions was completed in less than twenty-four hours. This method of administration is not reliable and the degree of diuresis obtained by its use does not approach that produced by the intravenous preparation.

II. Multiple Dose Method.—One to three tablets three times daily for a period of two to five days constituted a trial or course of treatment. Thirty-nine such courses were given to 29 patients. A satisfactory response was obtained in 25 trials (67 per cent), or 20 patients (69 per cent). Diuresis was usually slow in developing and in many patients did not reach its peak until the drug had been given for forty-eight hours. Nevertheless, the total diuretic response frequently approached that achieved with an intravenous preparation. This method is not the one of choice when rapid removal of edema fluid is desired. It is, however, the ideal method for patients who do not require emergency measures, for those who should have the edema fluid removed gradually, and for those who cannot be given the diuretic parenterally.

In considering the seemingly high percentage of failures in our study, it must be emphasized that in evaluating the effectiveness of any new drug, consideration must be given to concomitant therapeutic procedures. For this reason digitalis or ammonium chloride was deliberately withheld in several trials. We would undoubtedly have obtained a much higher incidence of effectiveness if the patients had been given these or other drugs. Our studies convinced us that previous digitalization and the maintenance of digitalis effects, as well as simultaneous administration of ammonium chloride, are desirable when an oral diuretic is used. We believe that unsatisfactory responses oc-

curred only in those patients who had a minimal degree of heart failure or in those whose heart disease was so severe that only a parenteral preparation could have resulted in diuresis. The use of the oral preparation is contraindicated when the response to the previous administration of a parenteral diuretic was unsatisfactory. Not only would the oral preparation be of no avail, but it might produce untoward reactions. Similar situations are encountered in the treatment of bronchial asthma with various epinephrine derivatives. For instance, epinephrine in oil cannot be expected to give relief when aqueous epinephrine hydrochloride has proved to be ineffective.

The slower diuresis produced by the oral mercurial administered by the multiple dose method is indicated in many patients. The oral method also enables the physician to treat patients to whom it is difficult to administer the drug by injection. Although the immediate diuresis may not be great, the effect of the oral Mercupurin may be more prolonged than that produced by the parenterally administered drug. Thus, patients who reaccumulate edema rapidly and for this reason require intravenous medication at frequent intervals, may accumulate their edema at a much slower rate, or not at all, when given the oral preparation. A diuretic with a slow but definite diuretic effect seems to allow the patient's heart to compensate to a greater degree.

The multiple dose method has particular value in the treatment of ambulatory patients. For those patients who require a mercurial diuretic only occasionally and whose congestive heart failure is not too severe, the use of the oral preparation makes fewer clinic visits necessary. The dose and scheme of administration must be determined for each patient. Once these are established, the patient readily learns the most propitious time for self-administration of the tablets.

In 10 of the 13 ambulatory patients studied, the response was considered to be satisfactory. Out of 152 trials, only eight resulted in an ineffective response. However, it should be remembered that the majority of the trials were in patients whose initial responses were favorable, and the drug was, therefore, continued as required. Thus, two patients (3 and 7, Table II[1]) with advanced rheumatic heart disease have taken 32 and 44 courses, respectively, and have remained very well controlled as ambulatory patients for over two years, while, with the use of the intravenous preparation, they had spent several weeks or months of each year in the hospital.

Toxicity with the multiple dose method was of little consequence in hospitalized patients. Mild gastrointestinal irritation of a transient nature was observed in only two of the 29 hospitalized patients. The ambulatory patient seemed more prone to develop gastrointestinal irritation, since it was noted in 6 of the 13 patients so treated. The characteristics of these reactions have been discussed in detail previously.[1] Such reactions do not usually limit the usefulness of the drug, since they may not recur upon repeated trials. No explanation for the higher incidence of gastrointestinal irritation in the ambulatory patients has been found. However, we have observed that many other drugs cause more untoward reactions in ambulatory patients than they do in hospitalized patients.

Evidence of kidney irritation was observed in only one of the 42 patients treated by the multiple dose method. This consisted of an increasing albuminuria after nineteen months of therapy which included 26 trials of one tablet three times daily for three-day periods. Since there was no evidence of generalized mercurialism and since the specific gravity of the urine revealed good concentrating ability, the presence of albuminuria was not considered to contraindicate the continuation of therapy.

III. Daily Dose Method.—The daily maintenance dose of Mercupurin administered orally was followed in 26 hospitalized patients for 30 trials and in 18 ambulatory patients for 31 trials. All of these patients were in progressively severe congestive heart failure which no longer responded to a maintenance dose of digitalis. With few exceptions all had been receiving frequent injections of Mercupurin intravenously. These injections brought temporary relief but did not prevent the reaccumulation of the edema. The 26 hospitalized patients received two tablets in an undivided dose for periods of seven to forty-one days (average period, nineteen days). The ambulatory group of patients have, to date, received from one to two tablets daily for periods of one to forty-nine weeks (average period, sixteen weeks) of continuous therapy. The patients of both groups were observed with and without the additional administration of ammonium chloride. In several instances the value of ammonium chloride was demonstrated by instituting its use after it was apparent that diuresis would not be produced by the administration of Mercupurin alone. It soon became evident that patients in severe congestive heart failure required several days of oral Mercupurin therapy before diuresis occurred. In those ambulatory patients who had been receiving Mercupurin intravenously at intervals of three to four days or a week, it was necessary to continue this regime until the oral drug became effective. To avoid undue overloading of the kidneys with mercury, it is recommended that no greater dose than 1 c.c. of the parenteral preparation be used. This procedure also avoids the tremendous diuresis, amounting in some patients to as much as 15 to 20 pounds of fluid, and the likelihood of complications or sequelae, which may occur when the usual parenteral dose is administered after the oral administration of 30 or 60 mg. of mercury for several days.

The patients who responded to the daily dose required from four to fourteen days (an average of seven days) of continuous therapy before the medication became effective. Of the 26 hospitalized patients complete removal of the edema and alleviation of acute symptoms such as paroxysmal dyspnea were obtained in 15 patients who had been previously uncontrolled. In four patients the diuresis was insufficient to alleviate completely the signs and symptoms of congestive heart failure, but definitely improved the cardiac status so that either intravenous mercurial diuretics were required less frequently or delayed the reaccumulation of the edema. An effective diuresis was, therefore, attained in 73 per cent of the hospitalized patients.

In the ambulatory group (18 patients) the results were even more gratifying, with effective diuresis being produced in 77 per cent of the patients. Ten patients with marked congestive heart failure, who attended clinic regularly

for weekly or biweekly injections of Mercupurin, became edema-free and presented minimal or no signs of decompensation. The status of four of the patients was improved: the edema did not reaccumulate as rapidly as before, and the necessity for intravenous mercurial diuretics was decreased.

The oral administration of Mercupurin failed in seven hospitalized and four ambulatory patients. Failure could be attributed in most cases to the severity of the heart condition, since eight of the 11 patients died shortly thereafter in spite of all efforts to induce diuresis. All eight of these patients also stopped responding to the intravenous mercurial diuretics. When a parenteral preparation no longer induces an effective diuresis, it is only natural to try other means of therapy. However, for such patients oral Mercupurin is of no value, and its use may result in mercurialism. Other reasons for failure were insufficiently long periods of treatment and the omission of the simultaneous administration of ammonium chloride.

Toxicity associated with the daily dose assumed several forms. The most common untoward reaction was digitalis toxicity related to the phenomena of mobilization of the digitalis from the edema fluid at the time of diuresis.[5] Thus, digitalis toxicity invariably occurred after diuresis was well established, i.e., after four to fourteen days of daily dosage, when the existing edema was in the process of being removed. Digitalis toxicity was observed in five of the hospitalized patients (19 per cent) and in six of the ambulatory patients (33 per cent); 11 of the 44 patients (25 per cent) receiving the daily dose. The classical signs of digitalis toxicity were observed. The rhythm changed from normal sinus rhythm to auricular fibrillation (four instances); there was a marked slowing of the ventricular rate of an underlying auricular fibrillation (four instances); A-V conduction time, as measured by the P-R intervals, increased to the level of partial block (two instances). However, when there was anorexia, nausea, vomiting, or diarrhea, it was difficult to decide whether the disturbance was due to gastrointestinal irritation from the oral Mercupurin or was a symptom of digitalis toxicity. Proof that these reactions were caused by digitalis toxicity was obtained when it was found that the gastrointestinal symptoms of all these patients subsided completely when digitalis was discontinued or decreased, even though the oral Mercupurin was administered uninterruptedly. Therefore, all patients presenting gastrointestinal symptoms, whether or not they presented the classical unequivocal signs of digitalis toxicity, were subsequently treated with smaller maintenance doses of digitalis. We have no doubt that true gastrointestinal irritation caused by the daily dose of oral Mercupurin may be encountered, although it was not observed in our series of patients.

Of more importance is the early recognition of mercurialism. Gastrointestinal symptoms associated with increasing albuminuria occurred in three instances. This occurred usually within a few weeks of the institution of therapy and only in patients who had already presented evidence of kidney disease. In one of these three patients these symptoms were associated with severe gingivitis and elevation of the nonprotein nitrogen. All of these manifestations subsided when the diuretic was discontinued. Four other patients presented in-

creasing albuminuria, but only after continuous therapy for more than thirty weeks. Fear of impending generalized mercurialism prompted the cessation of therapy in these four patients. However, they returned to the clinic or hospital in such severe congestive heart failure that administration of the oral diuretic was reinstituted in spite of the albuminuria. None of these patients demonstrated other signs of mercurialism. Not only did they continue to have a favorable diuretic response, but, even after additional therapy for as long as twenty weeks, they did not develop additional toxicity. Our experience with these patients and with many other patients who presented albuminuria before therapy was begun but did not develop further toxicity, leads us to believe that albuminuria per se does not contraindicate the continuation of the use of mercurial diuretics. These patients should, of course, be carefully observed for early signs of generalized mercurialism. It is our present policy, after the maximum effect of the oral diuretic has been achieved, to allow the patient a rest period of one week, and then to continue the diuretic for one month. Short rest periods are given between each monthly course.

Mild gingivitis was observed in four patients (9 per cent, including the patient already discussed). The gingivitis subsided promptly when therapy was discontinued. Two of the patients, given the oral therapy a second time, did not develop toxicity.

The most serious complication was the occurrence of uremia. The nonprotein nitrogen became elevated in two of the hospitalized patients. Following thirty-two days of continuous therapy, the first patient (already discussed) had a rise of the nonprotein nitrogen to 52 mg. per cent. After twenty days of continuous therapy the second patient, a 70-year-old woman with arteriosclerotic heart disease, became stuporous. This was associated with nausea, vomiting, and elevation of the nonprotein nitrogen to 112 mg. per cent. Prior to the appearance of these symptoms, a good diuresis had been obtained, in spite of a fixation of specific gravity of the urine. When the medication was discontinued, the nonprotein nitrogen returned to normal limits, but the patient reaccumulated the edema. A second trial consisting of twelve days of therapy again produced diuresis and an elevation of the nonprotein nitrogen to 90 mg. per cent. At no time did the patient show albuminuria or gingivitis. In the light of this experience, we believe that the oral mercurial should not be used in any patient who presents impaired kidney function, such as fixation of urinary specific gravity.

COMMENTS

The results indicate the value of the maintenance dose of Mercupurin administered orally in the treatment of patients with congestive heart failure. We feel that the effectiveness of the method outweighs the possibility of the occurrence of toxic reactions. It has its greatest usefulness in patients with congestive heart failure who have exhausted the value of a maintenance dose of digitalis and who, in spite of repeated injections of a mercurial diuretic, reaccumulate their edema or experience a recurrence of acute symptoms. The oral diuretic will remove all signs and symptoms of failure in such patients

making it possible either to dispense with the intravenous preparation or to decrease the number of injections required. We have never been able to achieve these results with any of the oral xanthine derivatives. Only since we have been using mercurial diuretics orally have we been able to improve the general status as well as the morale of patients with severe congestive heart failure and to make these patients continuously comfortable.

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MASSIVE LEFT AURICLE WITH SPECIAL REFERENCE TO ITS ETIOLOGY AND MECHANISM

Report of a Case

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MASSIVE dilation of the left auricle of such an extent that this chamber actually formed a part of the right border of the heart was described in 1901 by Owen and Fenton.[1] Since that time, there have been a number of such cases reported.[1-17] In reading these various papers we have been impressed chiefly with the various suggestions as to the possible causes of such enormous left auricles and the apparent benign course that the disease takes before heart failure appears.

The heart in the case that we wish to report, while similar to others discussed in the literature, is apparently one of the largest recorded, weighing 1,600 grams and containing over 2,000 c.c. of blood. Hearts weighing over 1,000 grams are considered rare since less than 50 cases have been recorded in the literature in the last one hundred years.[18] The relatively few reported cases are not, however, an accurate measure of the frequency of large hearts. Large hearts are not infrequently seen in any large autopsy service; one of us (H. S. M.) has in the museum of the Newark City Hospital a rheumatic heart with aortic regurgitation and mitral insufficiency weighing 1,250 grams, a syphilitic heart with aortic regurgitation weighing 1,160 grams, an hypertensive heart weighing 900 grams, and a heart with primary sarcoma weighing 1,500 grams.

Massive left auricle is considered by most authorities as a rare or unusual condition. We believe, however, that it is more frequent than thought to be.

CASE REPORT

History.—W. M., a 33-year-old white man, while sitting quietly at home, suddenly complained of substernal pressure, gasped, and died within a few minutes. When 8 years of age he had had his first attack of rheumatic fever, with a typical migratory polyarthritis involving most of the joints of his extremities. Between the ages of 8 and 14 years he had had recurrent, mild attacks of arthritis every spring. These illnesses usually lasted about two months and gradually cleared up with the approach of summer. When he was 10 years of age his tonsils were removed, although he had had no sore throats or frequent colds. When he was 15 years of age an infected supernumerary tooth in the left upper jaw was removed along with a portion of the bone which was also infected. After this operation,

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all arthritic attacks ceased, except for slight stiffening in one joint or another during damp weather. The patient was told at this time that his heart was affected. However, he had no cardiac symptoms. At the age of 15 he became a plumber's apprentice and, after four years, a journeyman plumber. During the next five years he engaged in amateur boxing, taking on bouts almost weekly without undue dyspnea or fatigue. He ran 5 or 6 miles two or three times a week without any difficulty. When 18 years old he ran to the top of the Washington Monument in fifteen minutes. His only reaction at the end of the climb was slight shortness of breath for several minutes and marked fatigue of his legs for about half an hour.

At the age of 29 he first began to have difficulty with his heart. He developed a short, hacking, nonproductive cough which he attributed to cigarettes. On one occasion he coughed up a small amount of bright red blood and was hospitalized for five days. His cough then ceased, and he returned to work. When 31 years of age he began to be dyspneic on slight exertion, and slight edema of the ankles appeared. After three days of particularly strenuous work which involved the use of a 15-pound sledge hammer, he developed severe dyspnea and orthopnea with generalized edema. This condition improved considerably after two weeks rest in bed, and he returned to work. In a short time, however, he had another severe break in compensation which necessitated two and one-half months of bed rest and digitalis therapy. After this episode breathing began to be associated with sharp, severe pains which radiated up and down the sternum. He also became conscious of his heartbeat. To make matters worse, the patient developed difficulty in swallowing with the result that two or three minutes were required for a bolus of food to pass through the esophagus.

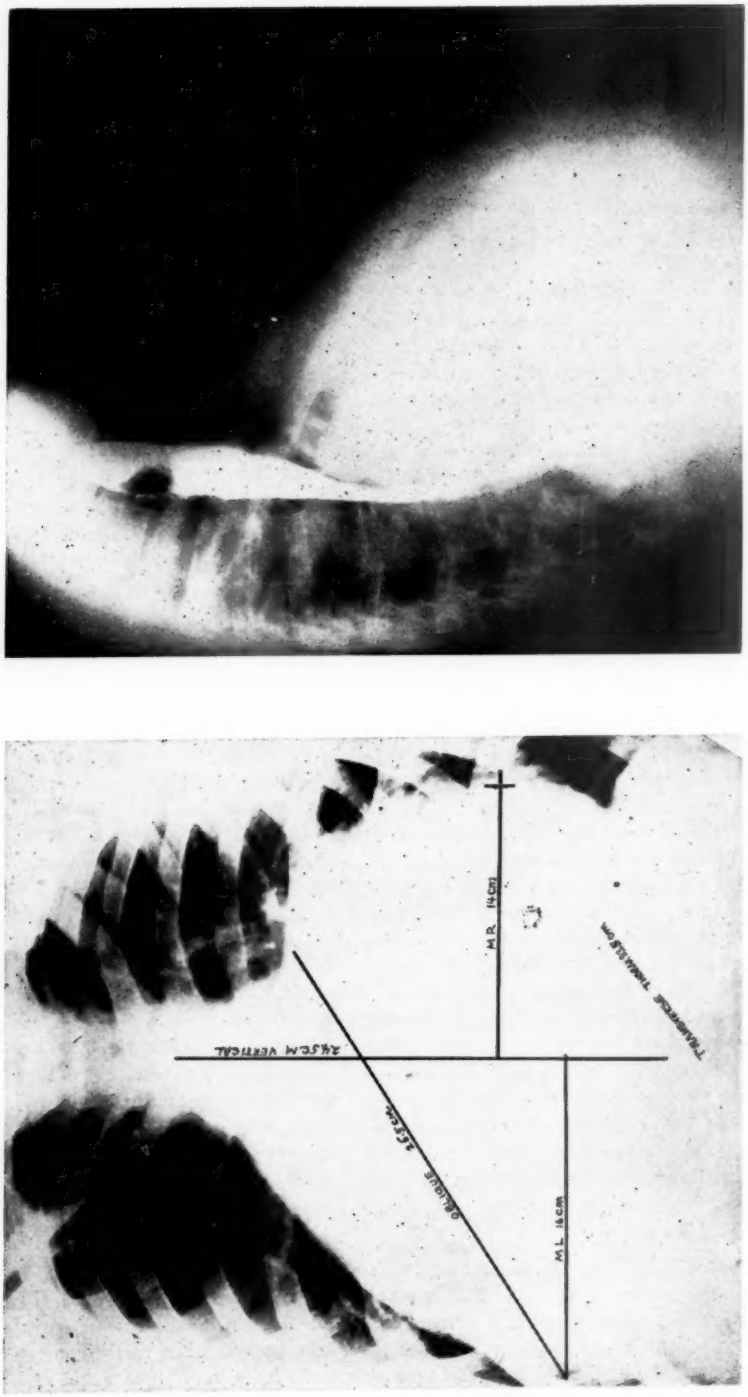
Six months after the onset of cardiac symptoms, the patient was admitted to the Newark Beth Israel Hospital.

Examination.—On initial examination the patient was sitting up in bed, and appeared to be fairly comfortable. There was no cyanosis, edema, or clubbing of the fingers. The blood pressure was 130/70 in both arms. The apex impulse was 16 cm. to left of the midline in the seventh intercostal space. A precordial heave was observed with each heartbeat. The heart sounds were of fair quality. Auricular fibrillation with a slow ventricular rate and no pulse deficit was present. A harsh, loud, systolic murmur was best heard in the region of the left nipple. The murmur was transmitted to the left axilla and down to the eighth rib in the anterior axillary line. This murmur obliterated the first sound but did not replace the second sound. About 1 inch below and to the right of the left nipple, this systolic murmur became musical and whistling in character and was heard to the midline. Just to the right and below the left nipple, a short, rumbling, loud presystolic mitral murmur was heard which was not transmitted. Over this same area a presystolic thrill was felt. Over the aortic area a short, musical, diastolic murmur, just preceding systole, was present. A very soft, short, blowing, systolic murmur was also heard in the same area. Over the tricuspid area a soft systolic murmur, replacing the first sound, was heard. Only occasionally was a systolic murmur elicited over the pulmonic area. Though these murmurs were generally demonstrable, they were not constantly present.

The remainder of the physical examination was essentially negative. During his stay in the hospital the temperature was normal, the pulse ranged from 40 to 88 per minute, and the respirations were 20 per minute.

The urine, blood count, and blood chemistry studies were normal, and serologic tests for syphilis were negative.

Subsequent Course.—After three months' stay in the hospital he was discharged as improved with the clinical diagnosis of "rheumatic heart disease with massive left auricle." During the next six months he had three attacks of decompensation which necessitated three short periods of hospitalization. In the intervals, he was kept fairly comfortable by small doses of digitalis and much rest and was able to do some very light work. His weight remained normal, he ran no fever, and he developed no anemia. Except for an occasional small hemoptysis and some substernal pain, which occasionally was severe and radiated to



A. *B.*

Fig. 1.—Teleroentgenograms showing massive left auricle. Anteroposterior and right lateral views.

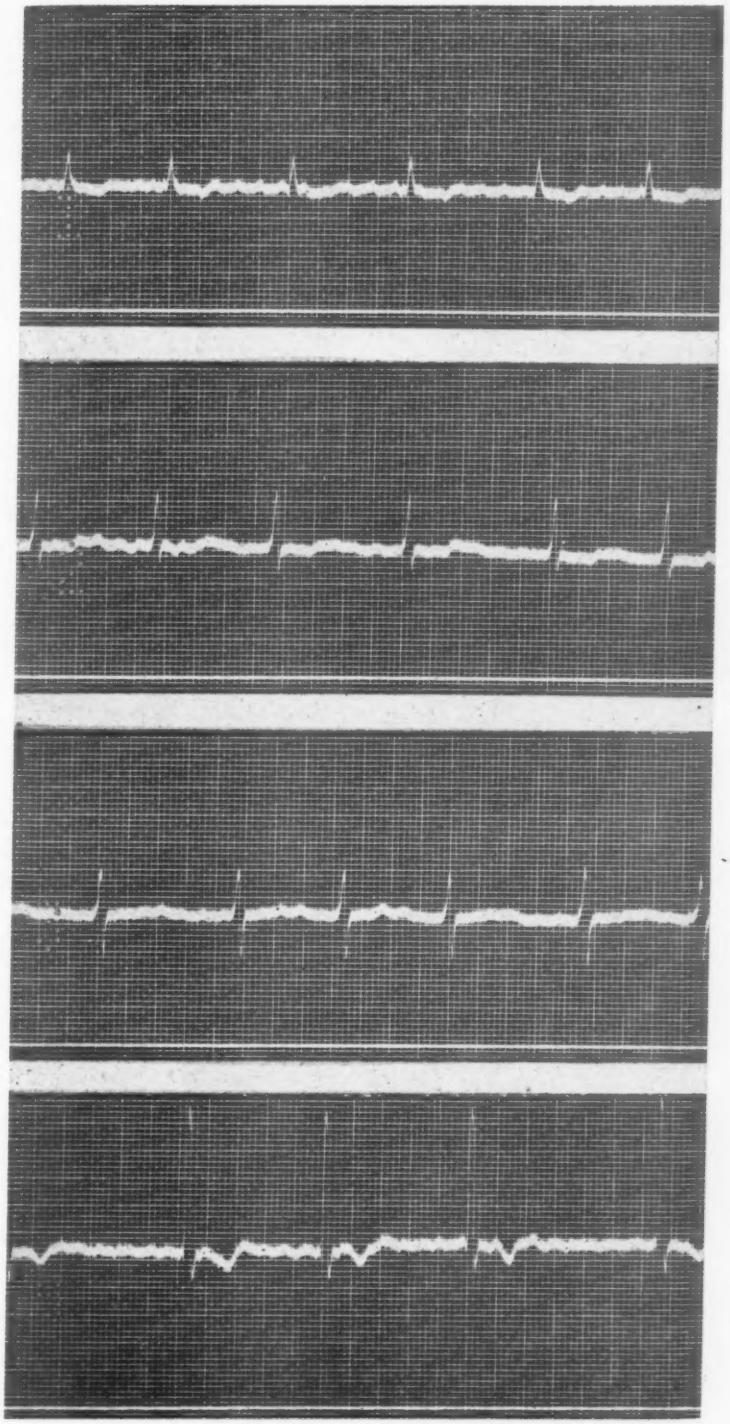


Fig. 2.—Electrocardiograms showing auricular fibrillation.

the left arm, he did quite well until his sudden death at the age of 33 years, three years after his heart first gave symptoms and 25 years after his original attack of rheumatic fever.

Autopsy.—The heart was found to be enormously enlarged, filling practically the entire chest. The heart contained over 2,000 c.c. of dark fluid blood most of which was in a massive left auricle. When opened and empty, the heart weighed 1,600 grams.

Gross Examination of Heart.—The heart was greatly enlarged and the visceral pericardium over all four chambers showed numerous loose tags of fibrous adhesions (Fig. 3). The striking feature was the size of the left auricle which was ballooned out into a large, thin sac, measuring 14 cm. in diameter. Most of the auricular wall was unusually thin and had an average thickness of 1 mm. (normal, 1 to 2 mm.), but at the top of the auricle near the auricular appendix the wall was 3 mm. in thickness (Fig. 3). The endocardium over most of the auricle was smooth and opaque, but above the posterior cusp of the mitral valve it was roughened, wrinkled, and thrown into small ridges and fissures (MacCallum's patch). On the posterior wall of the auricle there were two semilunar endocardial pockets consisting of fibrous thickening of the mural endocardium, with the concavities of these pockets pointed toward the pulmonary veins. The auricular appendix showed large and

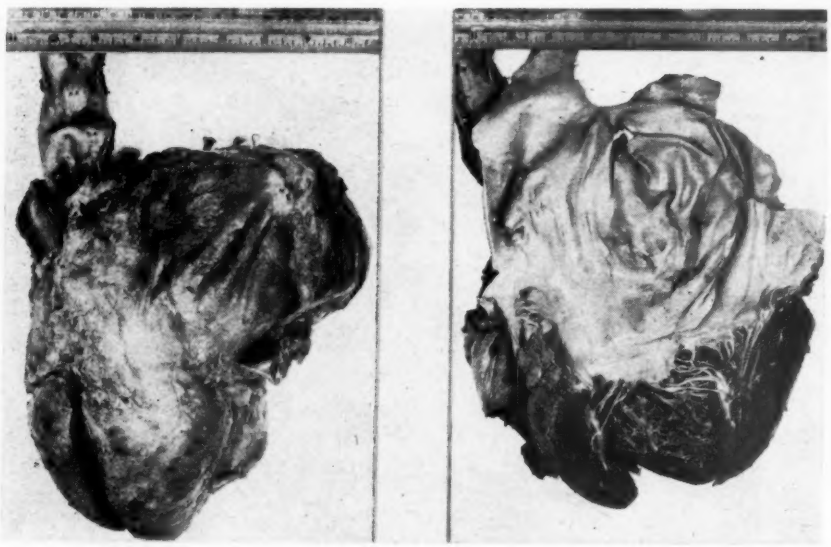


Fig. 3.—Heart showing massive left auricle, old pericardial adhesions, and a large, curled, rubbery mitral valve without stenosis.

hypertrophied trabeculae and was free from thrombus formation. The mitral orifice was larger than normal and, before the heart was opened, must have easily admitted over three fingers. The circumference of the mitral valve measured 13 cm. (normal, 10 cm.). Both leaflets of the mitral valve were diffusely thickened, opaque, curled, and rubbery in consistency. They contained no verrucae on their closure line and no fibrous ridges indicating healing of former verrucae. There was no calcification in the mitral cusps, *no predominant mitral stenosis,* and no annular sclerosis. The predominant anatomic valvular lesion was a mitral insufficiency. The chordae tendineae of the mitral valve showed no shortening but were thickened and unusually long, having an average length of 3 to 4 centimeters. There was no fusion at their origin or insertion. Both papillary muscles showed slight apical fibrosis.

The left ventricle was hypertrophied and measured 2.5 cm. in thickness (normal, 1.5 cm.). The myocardium showed no visible scarring and the septum was transparent and showed no subendocardial fibrosis. The aortic orifice measured 8.5 cm. in circumference

(normal, 7 cm.). The aortic cusps were normal and there was no verruca formation, fusion of cusps, or calcification. The orifices of both coronary arteries were normal in size. The lumen of the coronaries was patent throughout, and their intima showed only an occasional, soft, yellow placque which did not narrow the lumen. The aortic arch was elastic, of normal thickness, and showed no atheroma with the exception of two large hyaline placques near the orifice of the left subclavian artery. There was no syphilitic aortitis and no stenosis of the aortic isthmus. The descending aorta showed a few yellow streaks of atheroma.

The right auricle was greatly dilated and its walls were hypertrophied. The foramen ovale was closed. The right auricular appendix showed prominent trabeculation and contained no thrombus. The tricuspid orifice measured 12.5 cm. in circumference (normal, 12 cm.), and all three leaflets, while large, were normal in appearance and contained no verrucae. The chordae tendineae were delicate and not thickened.

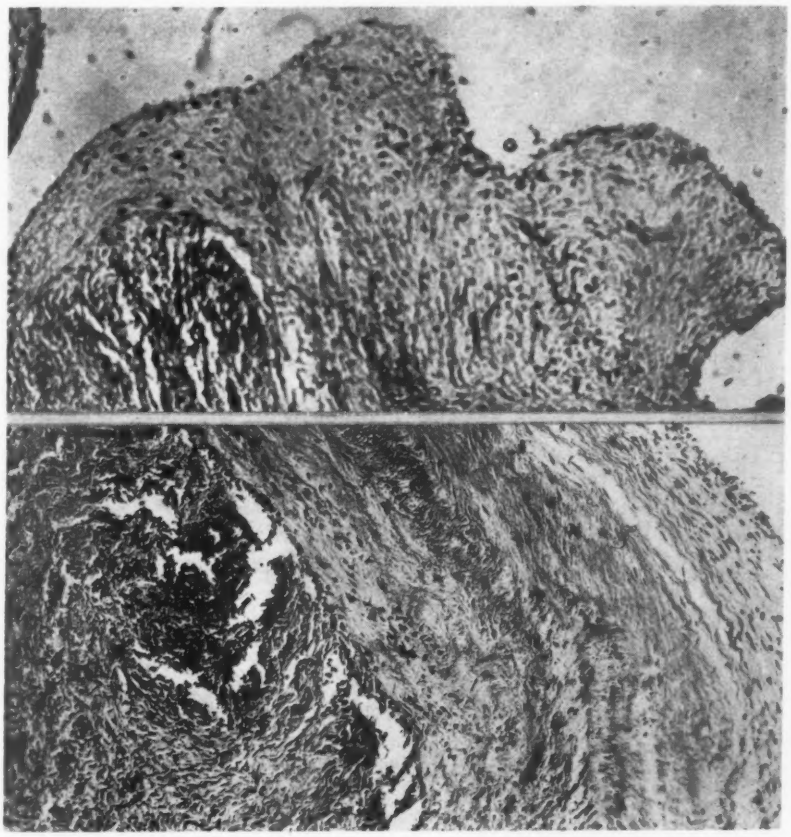


Fig. 4.—Rheumatic, interstitial mitral valvulitis. Curled mitral leaflets without verrucae.

The right ventricle was greatly dilated and hypertrophied, especially in the pulmonary conus, and measured 8 mm. in thickness (normal, 3 mm.). The columnae carneae were hypertrophied. The pulmonic valve circumference was 8 cm. (normal). The cusps were normal and showed no verruca formation. The pulmonary artery showed no atheroma and was normal in appearance.

Anatomic Diagnosis.—The anatomic diagnosis was rheumatic heart disease with massive left auricle without mitral stenosis and chronic passive congestion of lungs, spleen, liver, and kidneys.

Histologic Examination of Heart.—The pericardium showed marked thickening due to acellular fibroblastic tissue, in which there were numerous capillaries and many areas of hyalinization. No calcification was present. The deeper portions of the visceral pericardium contained many elongated spaces lined by low cuboidal mesothelium representing remnants of the pericardial cavity isolated during the stage of active inflammation. *Diagnosis: healed (inactive), rheumatic pericarditis* with fibrous pericardial adhesions.

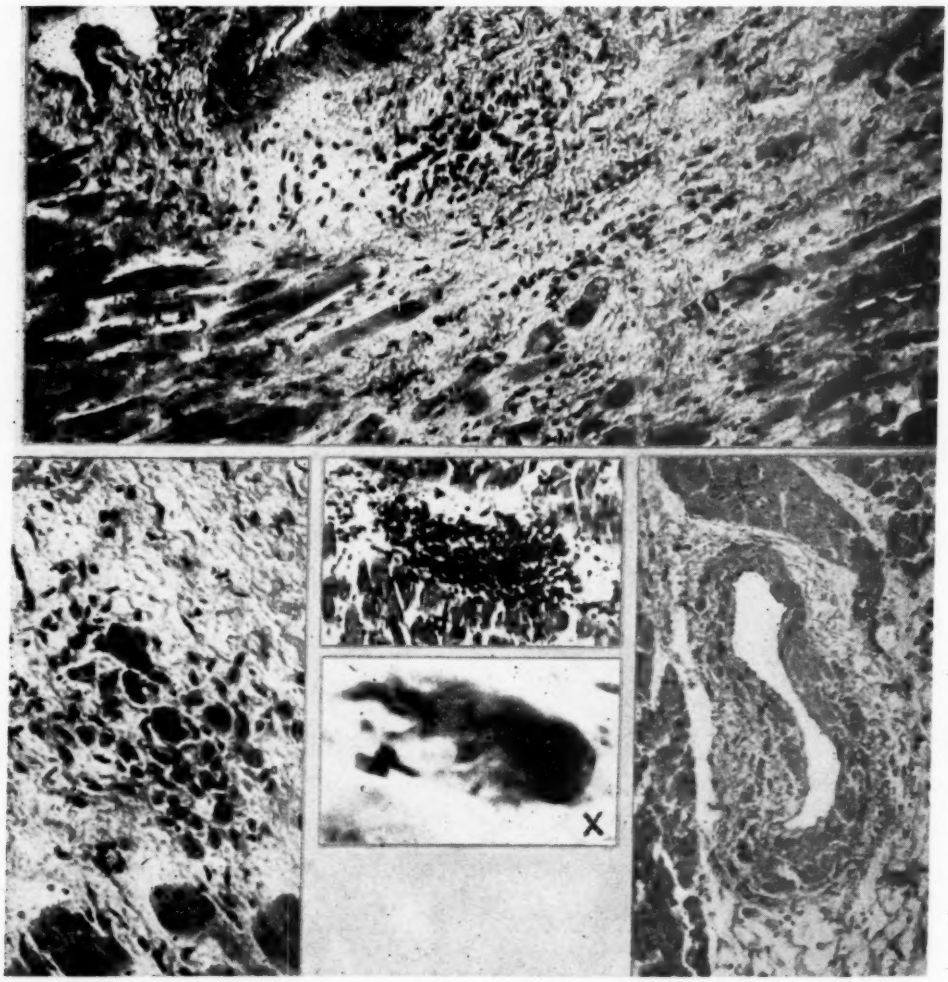


Fig. 5.—Myocardium showing hypertrophy, extensive scarring Aschoff bodies, lymphocytic infiltration, rheumatic arteritis, and at (*X*) calcium deposits in individual muscle fiber.

The left ventricle showed hypertrophy. Most of the muscle fibers were increased in length and width and contained hyperchromatic nuclei with blunt ends. Many areas contained a fine acellular fibrosis between muscle bundles and even between individual fibers. A rare muscle fiber showed bluish staining of the cytoplasm suggesting calcification. The arteries in the interstitium often were surrounded by triangular acellular scars; many represented healed Aschoff nodules. Aschoff bodies in various stages of development could be found without difficulty. Numerous areas of lymphocytic infiltration occurred in the interstitial tissue near larger vessels, but there were no polymorphonuclear or eosinophilic leucocytic foci. Many of the smaller arteries showed definite endovascular thickening but

no typical arteritis verrucosa was found. *Diagnosis:* combination of *healed (inactive)* and *chronic (active) rheumatic myocarditis* with marked *hypertrophy.* Healing predominates.*

The mitral valve showed considerable interstitial fibrosis composed of hyalinized, acellular collagen with overlying intact but wrinkled endothelium. Arterioles were numerous at the bases of leaflets, and new capillaries extended into the cusps. No calcification was present. There was no verruca formation. Toward the central portions of the cusps numerous areas of granulomatous infiltration consisting of lymphocytes, polymorphonuclear leucocytes, and a few eosinophiles were seen. *Diagnosis: healed (inactive)* and *chronic (active) rheumatic valvulitis* with inactive lesions predominating.*

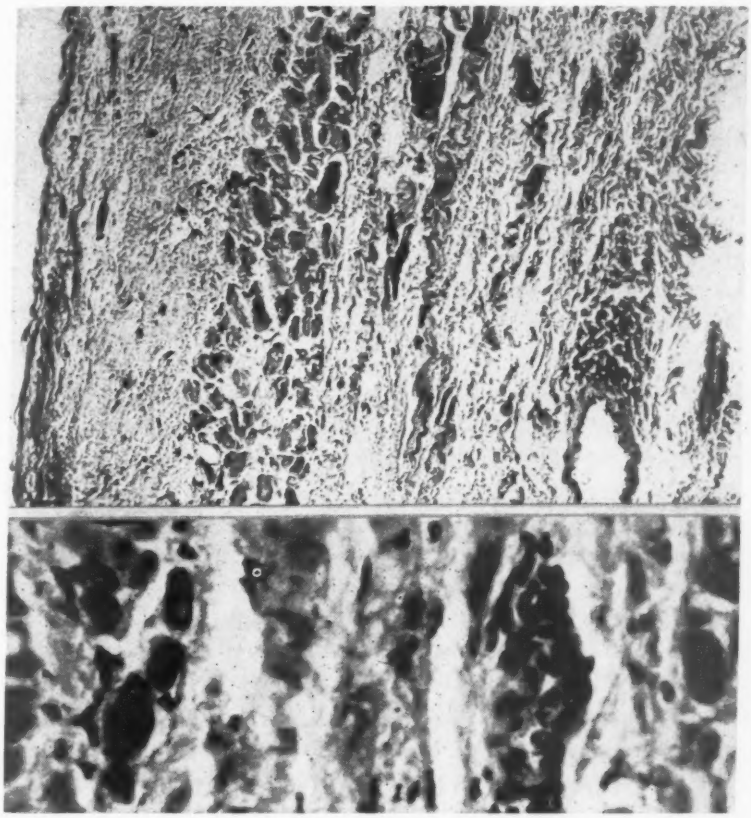


Fig. 6.—Left auricle showing extensive rheumatic auriculitis. Marked muscle atrophy, necrosis, fibrosis, and cellular infiltration may be noted.

The left auricle was the seat of the most extensive damage. Most of the auricular wall was thinner than normal due to marked muscle atrophy. The endocardium was intact, with an occasional histiocyte. There was marked thickening of the subendocardium due to great increase in acellular connective tissue. Between the subendocardium and the muscularis, atypical Aschoff bodies were easily recognized, consisting of cells with sharply defined nuclei with basophilic cytoplasm.

The muscularis showed great damage. Areas of muscle necrosis without much inflammatory reaction were frequent. This resulted in isolated, greatly hypertrophied muscle fibers with large, hyperchromatic nuclei. The adventitia showed marked perivascular lymphocytic

*The terminology used here conforms to that of the Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, New York, 1940.

infiltration and many of the smaller arteries showed marked endarteritis with thickened walls. Polymorphonuclear leucocytic foci were infrequent. The thicker parts of the auricular wall near the appendix showed muscle tissue, well preserved with an occasional area of calcification. *Diagnosis:* combination of *healed (inactive)* and *acute rheumatic auriculitis,* involving most of the auricular muscle and producing marked dilatation and thinning of the auricle.*

The *aorta* showed no definite rheumatic lesions. There were occasional subintimal lipoidal deposits. The adventitia was normal and free from lymphocytes.

The lungs, spleen, and liver showed only chronic passive congestion.

DISCUSSION

Mode of Production of Massive Left Auricle in Case Reported.—Examination of the heart leaves no doubt that death was due to severe rheumatic heart disease in various stages of activity and healing. Since there was no evidence of predominant mitral stenosis, the massive left auricle can be best explained on a mechanical basis somewhat similar to that which occurs in muscular insufficiency of the mitral valve. Mitral insufficiency without an accompanying stenosis is a rather unusual lesion in rheumatic heart disease. Osler[19] stated that, "Except in children, we rarely see the mitral leaflets curled and puckered without narrowing of the orifice."

We are of the opinion, therefore, that the chronological events in this case were somewhat as follows:

1. Rheumatic valvulitis of the mitral valve and at the same time or soon after a rheumatic carditis initiated the development of the lesion.

2. As a result of this inflammation the muscle of the left ventricle was weakened and a certain amount of dilatation occurred. The rheumatic process also produced an interstitial valvulitis of the mitral valve. This involvement did not produce stenosis, verrucae, shortening and fusion of chordae tendineae, fusion of the cusps, or calcification. It did, however, produce rubbery, curled, and puckered leaflets. This deformity of the leaflets together with the marked dilatation of the mitral ring resulted in improper closure of the valve and mitral insufficiency. The subsequent developments followed the course which was clearly described by Osler.[19]

3. The imperfect closure of the mitral valve allows a certain amount of blood to regurgitate from the ventricle into the left auricle so that at the end of auricular diastole this chamber contains not only blood which it has received from the lungs, but also that regurgitated from the left ventricle. This necessitates dilatation and, as increased work is thrown upon it in expelling the augmented contents, hypertrophy of the left auricle.

4. With each systole of the left auricle a larger volume of blood is forced into the left ventricle, causing a certain amount of dilatation and hypertrophy (the left ventricle does not hypertrophy normally in mitral stenosis unless there are lesions on the aortic valve).

5. During the diastole of the left auricle, as blood is regurgitated into it from the left ventricle, the pulmonary veins are less readily emptied. In consequence the right ventricle expels its contents less freely and in turn becomes hypertrophied and dilatated.

6. Finally, the right auricle also is involved. Its chamber enlarges and its walls increase in thickness.

7. In this case which we are discussing, this whole sequence of events was made much worse by the extensive auriculitis in the left auricle which shows rheumatic lesions of greater severity than any other part of the heart. Once dilatation of the left auricle began, the condition of this chamber became progressively worse until it finally became an enormous sac possessing very little contractility.

This result was undoubtedly contributed to by undue physical exercise between the ages of 15 and 20 years.

It is astonishing how long such a patient may live before congestive failure sets in, but the whole sequence of events is slow and compensation is maintained by hypertrophy of both ventricles.

Previous Explanations of Massive Left Auricle.—Most authorities agree that massive left auricle is unusual and that its development depends on the following factors: that because of its thin walls the left auricle is more capable of dilatation than the other chambers of the heart; that the left auricle has no safety valves such as the great veins give the right auricle; that whenever mitral disease is present the left auricle is bound to be filled by both ventricles since even with mitral stenosis there is combined insufficiency; and that any lesion or disease capable of causing increased left auricular pressure can be the underlying factor in the production of massive left auricle.[2-15]

The literature, however, often fails to give a clear conception of the cardiac pathology associated with massive left auricle, the predominant lesion of the mitral valve, whether stenosis or insufficiency, and the condition of the auricular wall.

Rheumatic heart disease is considered by most observers as the type of disease in which most of these enormous left auricles occur. Many reports, however, fail to show which portions of the heart are most affected and whether active rheumatic lesions are present.

Causes other than valvular disease have been cited in a few cases. Peel,[17] observed marked dilatation of both auricles in a case showing no valvular disease and considered it as secondary to heart block. Dialer[16] showed that tuberculous fibrosis of the auricular musculature might result in massive left auricle.

Mitral stenosis is assumed by most authorities to be the main factor in the production of massive left auricle. There is no doubt that tight mitral stenosis, such as occurs in chronic valvular defects due to rheumatism or localized arteriosclerosis, is often followed by hypertrophy and dilatation of the left auricle. The auricle may reach a considerable size. White[20] states that in mitral stenosis "the left auricle, being affected first, may assume enormous proportions, and cases are on record in which its bulk was larger than that of all the rest of the heart, its capacity increasing even to 1,000 c.c. or more (normal about 125 c.c.)." If this is true, some of these auricles have reached a size sufficient to be regarded as "massive." However, in over 15,000 autopsies by one of us (H. S. M.), we have never encountered predominating mitral stenosis which produced really massive left auricles.

In the cases reported by Owen and Fenton,[1] Emanuel,[2] and Bach and Keith,[15] there was no mitral stenosis but only dilatation of the mitral valve. In a case reported by Bishop and Babey,[13] in which the left auricle was 12 cm. in diameter and held 1,550 c.c. of water, there was a rheumatic mitral valvulitis with only a small degree of mitral stenosis. The mitral valve measured 9 cm. in circumference. Microscopic examination of the left auricle "was characterized by a marked thinning of the muscle layer, the myocardium occupying but a small proportion of the entire thickness."

There is therefore considerable evidence in the literature to support our contention that predominant mitral stenosis is not a factor in the production of these enormous left auricles. If it were, massive left auricle would be more frequently encountered.

Fibrosis of the left auricle has been mentioned in only a few cases as one of the most important factors in the production of massive left auricle. Most reports do not specifically mention the predominance of rheumatic lesions in the left auricular wall and the presence of a rheumatic auriculitis. Bramwell and Duguid,[10] and later Nichols and Ostrum,[12] first suggested that in massive left auricle there was more evidence of rheumatic myocarditis with fibrosis in the left auricle than in any other part of the heart. Once the left auricle becomes fibrotic, it is only necessary that the left ventricle be competent and capable of exerting a sufficient back pressure and the auricle will then begin to dilate.

Clinical Features.—The symptoms and findings in our cases are more or less typical of the entire group. Most of the massive left auricles occur in rheumatic heart disease. Various murmurs are heard and varying amounts of dullness on percussion of the cardiac outline are present depending on the degree of auricular enlargement. Pain in the chest is common, more often on the right side. Difficulty and pain on swallowing are frequent, due to pressure and distortion of the esophagus by the large auricle. A dry, nonproductive cough is common.

Auricular fibrillation, though it is not always present, is very common. It is probably the result of the great amount of auricular damage due both to the rheumatic auriculitis and the great expanse of the auricular wall.

When the heart becomes large enough, heart sounds will be heard in the right axillary line as well as over the rest of the chest. Other symptoms will appear as failure or other complications occur.

The fluoroscopic and x-ray findings are characteristic. It is in the postero-anterior view that massive left auricle is usually recognized. As the heart is observed under the fluoroscope or viewed in x-ray films, there is on the right side of the heart a more dense shadow, to the right of which there is a less dense one; the so-called "double contour shadow." The dense shadow is the right auricle with the left auricle lying to the right of this portion of the heart. When the enlargement of the left auricle is not quite so great, the right border of the heart shadow looks like a double convex curve, with one arc above the other. The upper arc is the left auricle and the lower one is the right. In the right anterior oblique position, the enlarged left auricle of

rheumatic heart disease encroaches upon the mid-portion of the retrocardiac space. However, in these massive hearts there is more and more encroachment upon this space as the auricle enlarges. When the patient is given barium paste, the esophagus is readily seen pushed backward and to the right by the massive left auricle. There is usually delay in the passage of the barium.

Why the left auricle should appear on the right side of the heart is a controversial subject. Nichols and Ostrum[12] suggest that whenever the left auricle becomes enlarged there is also enlargement of the right auricle, thereby causing a rotation of the entire heart to the left. This results in the left auricle swinging to the right of its normal position. Since the left auricle cannot then enlarge to the left because it is unable to expand through the arch of the aorta, and since the spine blocks it from behind, the left auricle can only enlarge to the right, forward, and upward, producing the unusual picture seen in massive left auricle.

Steele and Paterson[21] have a slightly different concept to offer. They state that the anatomic position of the left auricle is normally uppermost and posterior. The tracheal bifurcation is just above it with the left main bronchus resting upon it and the esophagus passing right behind it. Therefore, because of its posterior position and anatomic borders, this part of the heart may enlarge either to the left or to the right. However, because of the fixed structures about it, once it gets beyond a certain point, the enlargement must of necessity be to the right.

One of the most interesting clinical aspects of massive left auricle is the remarkable physical capacity of these patients in spite of the tremendous cardiac enlargement. It has been suggested,[10-12] that the main positive factor in this cardiac reserve lies in the integrity of the heart muscle other than the left auricle. As a result, the ventricles are able to do their job in an adequate fashion as long as the auricles keep supplying them with blood. In these cases, because of the huge capacity of the enlarged left auricle, enough blood usually does get into the left ventricle in spite of the fact that the auricular contractions are poor and because there is no predominant mitral stenosis.

SUMMARY

1. Three main factors seem to be essential for the formation of most cases of massive left auricle: (a) *rheumatic carditis* over a long period of time, showing various phases of activity with predominant inactivity and healing during the last few years of life; (b) *mitral insufficiency* due to rheumatic myocarditis of the left ventricle in various stages of activity and healing and rheumatic valvulitis characterized by curled and rubbery mitral segments (in our experience, predominating mitral stenosis will not produce such massive auricles); and (c) *rheumatic auriculitis* in various stages of activity and healing with marked muscular atrophy and fibrosis, of such intensity that the left auricle is often more severely damaged than any other part of the heart.

2. The importance of an undue amount of physical exercise during the early stages of rheumatic heart disease, such as this patient indulged in, must

be stressed as a contributory factor in overdistention of the diseased left auricle.

3. Massive left auricle is perhaps not as unusual as we are led to believe. It has been observed in induction centers in men who have enormous hearts and who are in a fair state of health. It is characteristic of the lesion that individuals can be comfortable with no cardiac symptoms for a period of years before decompensation sets in.

4. It would seem that too much importance is placed by cardiologists on so-called "Combined Lesions" of the valves. In the case of the mitral valve it is widely held "that all stenotic valves have some regurgitation and all insufficiencies have some degree of stenosis." This concept seems to have developed in order to explain the presence of certain murmurs, often of little consequence. It has led to considerable confusion. Certainly at autopsy it is comparatively simple to determine whether stenosis or insufficiency predominates; it is also simple to determine that the various dilatations and hypertrophies due to valvular defects depend chiefly on the predominating lesion.

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THE EFFECT OF CERTAIN DRUGS UPON THE CARDIOTOXIC LESIONS OF DIGITALIS IN THE DOG

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IN A recent editorial in *The Journal of The American Medical Association*,[1] attention was drawn to the fact that digitalis preparations are capable of producing, among other toxic effects, myocardial lesions in experimental animals. This effect of digitalis has been described in many publications, the most noteworthy of which were contributed by Buchner,[2] Hu, Lieu, and Li,[3] La Dre,[4] and by Dearing, Barnes, and Essex.[5] In all reports, the cardiac changes resulting from digitalis administration have been similar. The lesions consist of areas of focal necrosis, fraying of the muscle fibers, fibrosis, hemorrhages, and cellular infiltrations.

Our interest in this work was stimulated by the fact that these pathologic changes are almost identical with those produced in dogs by Manning, Hall, and Banting[6] as a result of vagal stimulation, and by Hall and his associates[7] as a result of injections of acetylcholine iodide.

Since no evidence has been submitted as to the mechanism of how digitalis preparations are capable of producing myocardial lesions, our efforts have been made in an attempt to shed some light upon this problem.

PROCEDURE

Thirty-two young dogs were studied in this experiment. Seven animals received 2 or 3 cat units of digiglusin daily, depending upon the dog's tolerance to the drug. Five animals were given digiglusin plus 3¾ grains of aminophylline twice daily. Five dogs received digiglusin plus 3 grains of theobromine sodium acetate three times daily. Eight dogs were given injections of digiglusin plus 1½ grains of papaverine hydrochloride twice daily. Seven animals were treated with digiglusin and atropine sulfate. The latter drug was administered by mouth in tablets of 1/75 grain four times daily and in addition all water was atropinized with 1/65 grain to the liter. All animals were observed daily, and, when it was obvious that death was imminent, the dog was given an ether anesthetic and the heart was removed. Blocks of tissue were taken from the right and left auricles, anterior left ventricular wall, posterior left ventricular wall, lateral wall of the left ventricle, anterior right ventricular wall, posterior right ventricular wall, and the interventricular septum. Tissue was fixed in formalin and sections were made and stained with hematoxylin and eosin.

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RESULTS

All animals receiving injections of digiglusin alone developed microscopic myocardial changes. These consisted of areas of vacuolation of cells, focal necrosis and hyalinization, round cell and polymorphonuclear infiltrations, hemorrhages, and fibroblastic proliferation. These lesions are similar to those described by previous investigators.

The dogs receiving aminophylline and digiglusin developed only minimal and scattered lesions consisting of slight edema and loss of striations of the muscle fibers. Theobromine sodium acetate with digiglusin was admin-

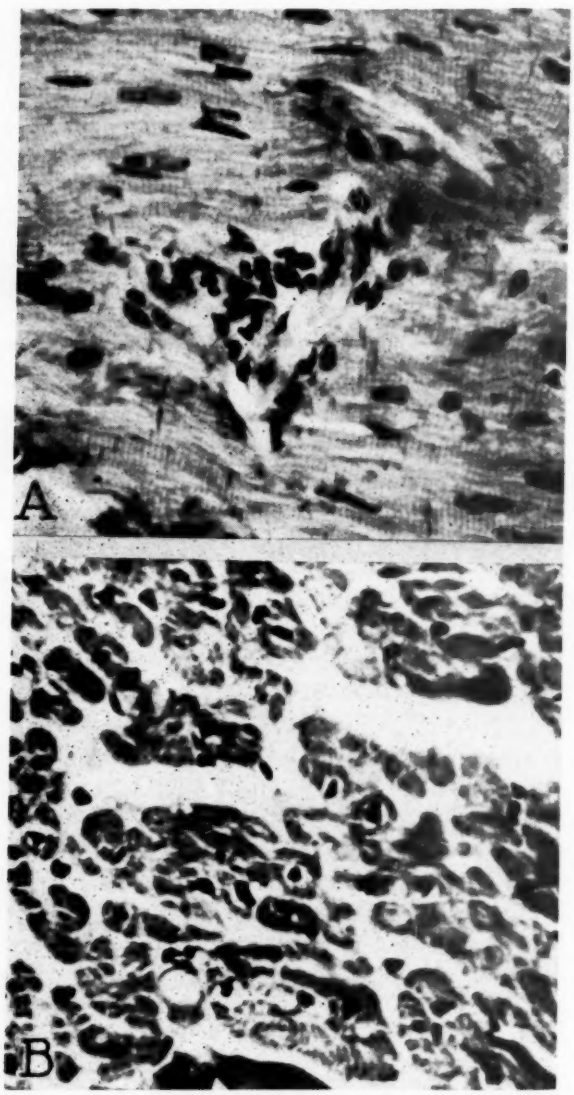

Fig. 1.—*A*, Dog 4. **Digiglusin alone. Round cell infiltration** (×660). *B*, Dog 2. **Digiglusin alone.** Vacuolation and necrosis of cells (×660).

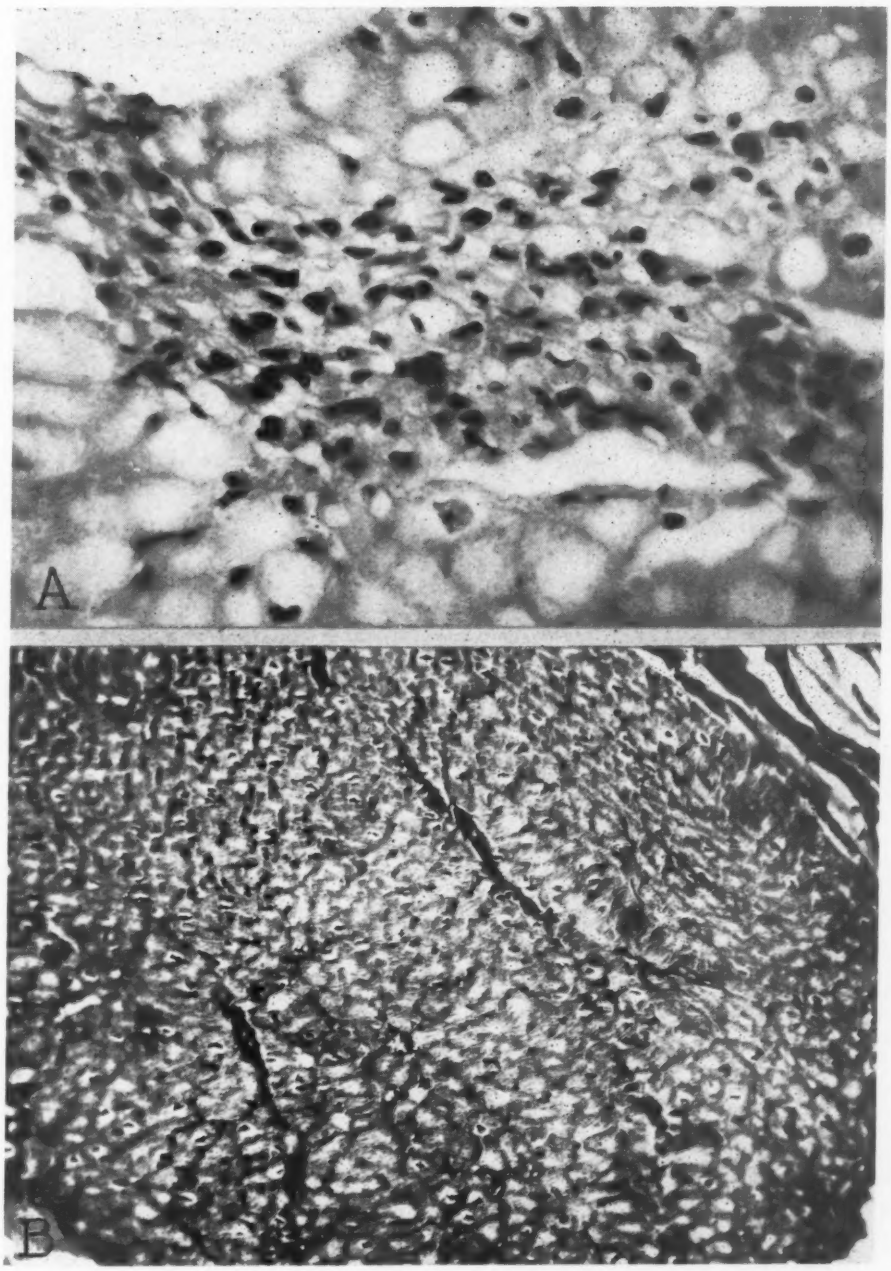

Fig. 2.—*A*, Dog 3. Digiglusin alone. Proliferation of fibroblasts (×800). *B*, Vacuolation of cells (×275).

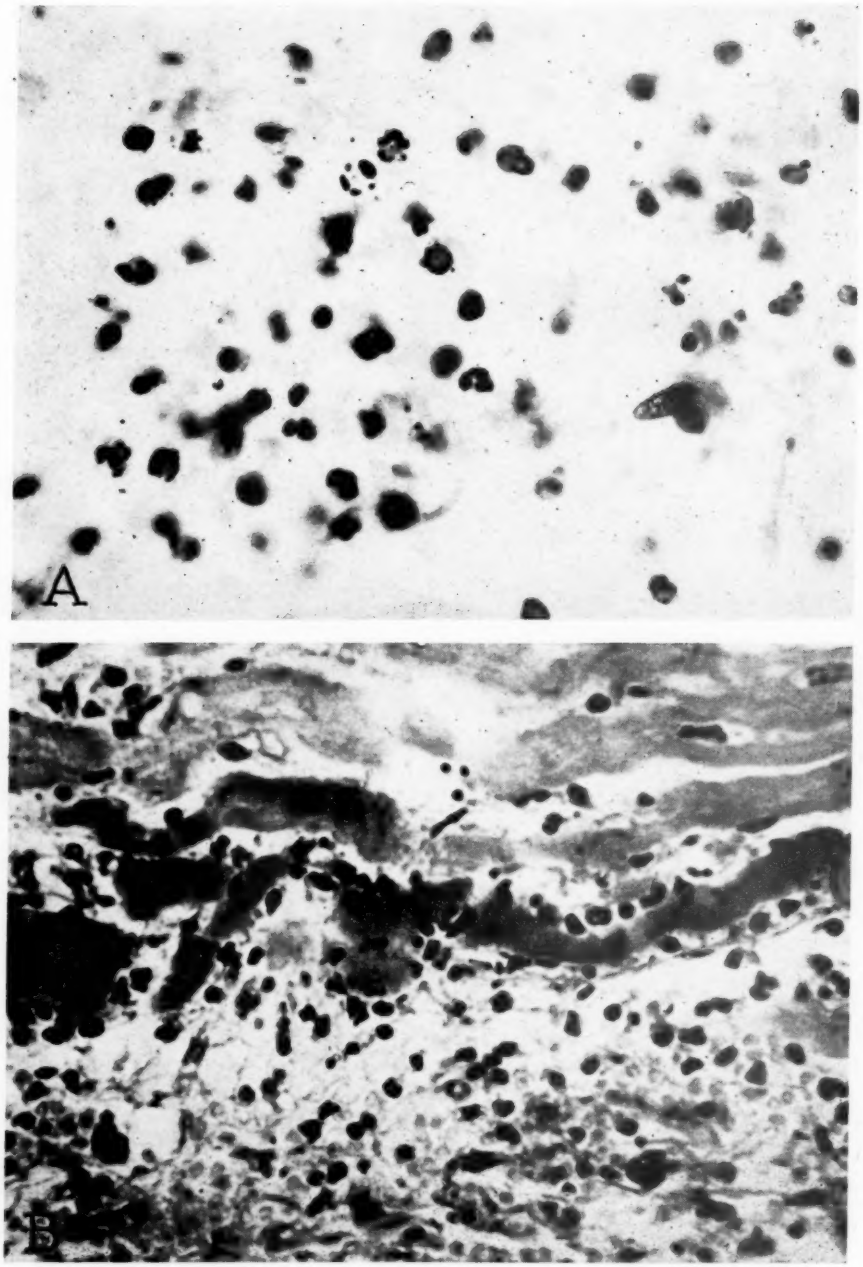

Fig. 3.—*A*, Dog 10. Digiglusin plus papaverine. Necrosis of cells with polymorphonuclear infiltration (×1030). *B*, Dog 10. Round cell infiltration (×304).

istered to five dogs. Three of these animals developed minor changes made up of occasional areas of vacuolation and polymorphonuclear infiltration. Two of the dogs that received theobromine had lesions equally as marked as those that received digiglusin alone.

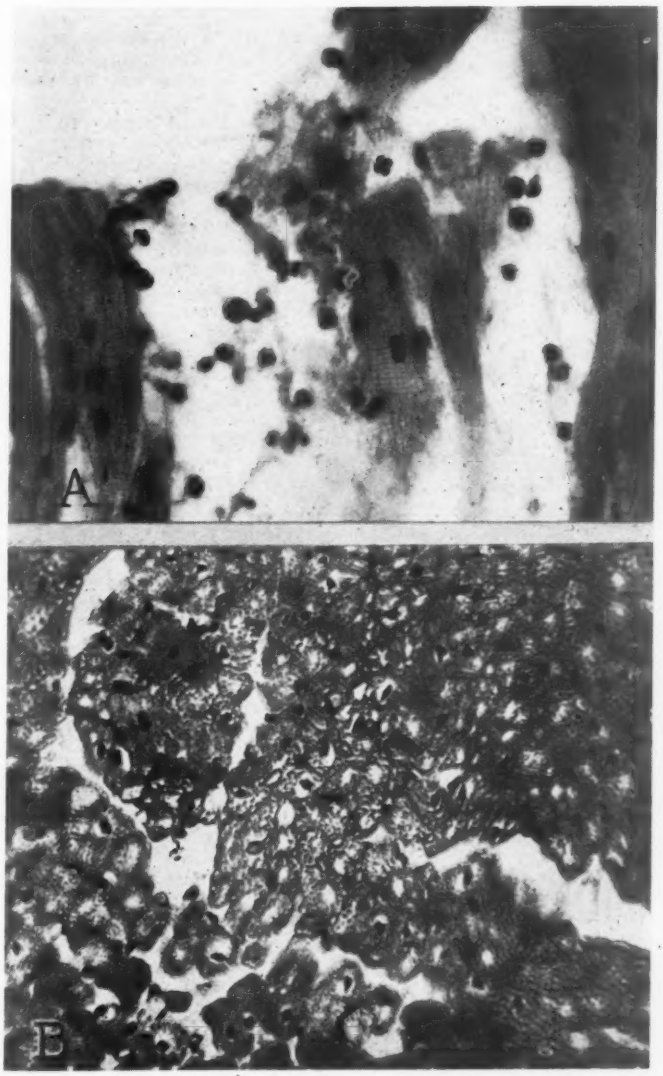

Fig. 4.—*A*, Dog 423. Digiglusin and papaverine. Polymorphonuclear and round cell infiltration (×660). *B*, Dog 405. Digiglusin and papaverine. Vacuolation of cells (×470).

Papaverine hydrochloride with digiglusin was injected into eight animals, seven of which revealed very marked myocardial abnormalities identical with those that were found in the animals receiving only digiglusin.

TABLE I. DATA OF DOGS RECEIVING ONLY DIGIGLUSIN

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (C.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
1	February 10 to May 6 86 days	144	Heart slightly dilated	Hemorrhage into muscle, mild hyalinization of fibers, fraying of fibers
2	February 10 to April 26 76 days	96	Normal heart	Round cell accumulations, hyalinization of fibers, vacuolation of fibers, loss of striations in fibers, fraying of fibers
3	May 28 to July 2 34 days	88	Heart mildly dilated	One area suggestive of infarction with fibroblasts, polymorphonuclear leucocytes, and necrosis. Vacuolation of fibers. Hemorrhages, highly cellular scar
4	June 28 to August 17 51 days	110	Heart mildly dilated	Scattered areas of polymorphonuclear leucocytes. Foci of lymphocytes, loss of striations of muscle fibers, edema of fibers
5	June 28 to August 20 54 days	119	Heart mildly dilated	Necrosis of fibers, hyalinization of fibers, edema, round cell infiltration
6	October 27 to November 23 28 days	67	Heart mildly dilated	Vacuolation of fibers, edema
7	October 27 to November 17 21 days	52	Normal heart	Necrosis of fibers, one small area of fibrosis, hemorrhages, small accumulation of polymorphonuclear leucocytes

TABLE II. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS AMINOPHYLLINE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (C.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
8	October 27 to November 22 27 days	64	Heart mildly dilated	Slight loss of striations in fibers. Congestion of vessels
9	October 27 to December 2 37 days	88	Heart mildly dilated	Normal myocardium except for a few pyknotic nuclei
441	January 17 to February 5 20 days	36	Normal	Normal myocardium. Venous congestion
444	January 17 to February 2 17 days	29	Normal	One area in which fibers were separated by fibrous tissue
449	February 3 to February 23 20 days	40	Normal	Slight edema of fibers. Distention of veins

Two of the atropinized animals developed definite cardiac changes. However, five dogs had hearts with only occasional areas of cellular infiltration and slight vacuolation of muscle fibers. The degree of these changes was much less than those in the animals receiving only digiglusin.

All data for the entire experiment are summarized in Tables I to V.

Figs. 1 to 4 are photomicrographs showing the pathologic changes described.

TABLE III. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS THEOBROMINE SODIUM ACETATE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (C.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
425	February 6 to March 7 29 days	61	Normal heart	Occasional area of polymorphonuclear infiltration, vacuolation, and fibroblastic proliferation
428	February 6 to March 7 29 days	61	Normal heart	Hemorrhage, polymorphonuclear infiltrations, vacuolation
430	February 6 to February 23 17 days	30	Normal heart	One area of polymorphonuclear infiltration
431	February 6 to March 9 31 days	64	Normal heart	One area of vacuolation and cellular infiltration
432	February 6 to March 9 31 days	64	Normal heart	Slight vacuolation

TABLE IV. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS PAPAVERINE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (C.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
404	September 25 to October 20 26 days	45	Normal	Areas of hemorrhage into muscle and areas of vacuolation
405	September 25 to November 10 47 days	90	Normal	Cloudy swelling, vacuolation of fibers, hemorrhages, few areas of polymorphonuclear infiltration
460	September 25 to November 14 51 days	100	Normal	Vacuolation, polymorphonuclear infiltration, hemorrhages into fibers, round cell infiltration
423	October 6 to November 29 55 days	114	Normal	Hemorrhages, polymorphonuclear infiltration, round cell infiltration
406	October 12 to November 29 49 days	102	Normal	Polymorphonuclear infiltration, round cell infiltration, areas of vacuolation
455	January 17 to February 12 27 days	53	Normal	Slight edema of fibers
437	February 9 to March 4 25 days	50	Normal	Vacuolation of fibers, necrosis, collections of round cells
10	October 27 to November 22 27 days	64	Mildly dilated	Marked necrosis, round cell infiltration hemorrhages

DISCUSSION

If, by experimental investigation, the mechanism of action of certain drugs can be more clearly elucidated, a definite contribution will have been made which will be of value both to the research worker and to the practicing physician. All of the preparations used in this study are frequently used in clinical medicine and, for this reason, the conclusions reached should be of definite value to those interested in treating heart disease.

It is obvious from the results of this study that certain drugs are capable of minimizing the cardiotoxic effects of digitalis. This fact gives a clue as to

TABLE V. DATA OF DOGS RECEIVING DIGIGLUSIN PLUS ATROPINE

DOG	DATES OF EXPERIMENT	TOTAL AMOUNT OF DIGIGLUSIN (C.C.)	GROSS FINDINGS	MICROSCOPIC FINDINGS
401	September 25 to November 14 51 days	98	Normal	One small area of vacuolation
418	October 6 to November 10 36 days	66	Normal	Vacuolation of fibers, round cell infiltration, polymorphonuclear infiltration
414	October 12 to November 29 50 days	105	Normal	Vacuolation of fibers, hemorrhages, polymorphonuclear and round cell infiltration
415	October 7 to November 24 48 days	112	Normal	Occasional polymorphonuclear accumulation. One small area of vacuolation
412	September 29 to November 24 57 days	120	Normal	Few areas of vacuolation, occasional areas of polymorphonuclear infiltration
462	February 24 to March 24 30 days	66	Normal	One small accumulation of round cells
438	January 17 to February 12 27 days	56	Normal	Few collections of round cells, slight vacuolation of fibers

the mechanism by which digitalis preparations are able to produce myocardial lesions. This harmful action of digitalis can be mediated in one of three ways: (1) by direct action of digitalis upon the myocardium; (2) by stimulation of the vagus nerve resulting in the liberation of acetylcholine, which substance produces coronary vasoconstriction; or (3) by a direct action upon the coronary arteries resulting in constriction of these vessels.

If the myocardium is injured through the first or third mode of action, then all of the animals in this experiment should have developed myocardial changes because all dogs received digiglusin. This did not occur and we therefore feel that the toxic action of digitalis is not a direct one.

Since atropine sulfate definitely minimized the cardiac changes which occurred, we feel justified in presenting the following hypotheses: (1) The cardiotoxic effect of digitalis in the dog is the result of vagal stimulation, which produces coronary constriction resulting in myocardial ischemia. (2) This specific result of digitalis administration may be modified by administering a drug which will overcome or prevent coronary artery constriction. In this work aminophylline, theobromine sodium acetate, and atropine sulfate were drugs which had this action. The former was the most efficient.

A rather surprising result of this work is the evidence that papaverine did not modify the effect of digitalis. Since the xanthine drugs were used in dosages which are usually employed clinically, it was felt that 1½ grains of papaverine hydrochloride given twice daily would be adequate for purposes of comparison. We have found no evidence in our experiments that indicates why papaverine was ineffective. Richards,[8] in some unpublished work, has evidence that the vasodilating effect of papaverine is very transient compared with that of aminophylline. This may explain the results we have obtained. It is also

possible that we did not use an adequate dose of papaverine. We feel, however, that in evaluating one drug with another comparative quantities must be used. It would seem unfair to compare the effect of papaverine with aminophylline if the usual clinical dose of aminophylline was evaluated against twice the clinical dose of papaverine. Further work on the vasodilating action of papaverine is now in progress, in which larger doses of this drug are being employed.

Theobromine sodium acetate is, in our opinion, more effective in effecting an increase in the coronary flow than is aminophylline. It is probable that giving the drug by mouth made some difference and that this also influenced the effect of the atropine.

SUMMARY

An experiment is presented in which it is shown that the cardiotoxic effects of digitalis in the dog may be modified by the use of aminophylline, theobromine sodium acetate, and atropine sulfate. Papaverine hydrochloride did not minimize the cardiac changes produced by digitalis administration.

A theory is discussed which could explain the results of this study.

CONCLUSIONS

1. Digitalis in toxic doses produces myocardial lesions in the dog.

2. Aminophylline and theobromine sodium acetate in doses usually employed clinically are capable of modifying this toxic effect of digitalis.

3. Aminophylline was more efficient than theobromine in preventing the myocardial lesions resulting from the administration of digitalis.

4. Atropine sulfate is capable of ameliorating the cardiotoxic effect of digitalis.

5. Papaverine hydrochloride, in the usual clinical dose, did not prevent the cardiac changes produced by the administration of digitalis.

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THROMBOPLASTIC PROPERTIES OF SOME MERCURIAL DIURETICS

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IN A PAPER read at a meeting of the American Medical Association in 1942, the present writer announced a pharmacologic discovery, which in the past three years has been followed by developments of considerable clinical importance.[1] It is for this reason that the present preliminary announcement is being published. At the A.M.A. meeting it was reported that, when repeated samples of blood are taken from cats during intravenous injections of digitalis or ouabain solutions for purposes of assay, the coagulation time of the blood samples as determined by Howell's method progressively shortens. This phenomenon did not occur in control experiments. The same phenomenon of marked decrease in coagulation time was observed following the administration of digitalis to rabbits, when the blood samples were obtained by direct heart puncture. This thromboplastic effect was also produced in vitro, not only by digitalis and ouabain, but also by all digitaloid glucosides which we were able to obtain. Numerous other drugs were used as controls. With but few exceptions these drugs did not bring about a decrease in coagulation time; the most outstanding exception was epinephrine. These findings were corroborated by Werch[2] on rabbits; and still further by de Takats, Trump, and Gilbert.[3] The latter authors stressed the clinical significance of the phenomenon, because they regarded it as the most plausible explanation of sudden death in patients under digitalis therapy, who unexpectedly develop thromboembolic accidents. Recently these findings have been still further corroborated.[4]

In 1943, the author amplified his original findings in a report made before a joint meeting of the American Therapeutic Society[5] and the Southern Medical Association[6] and ventured to predict that other drugs might exhibit similar thromboplastic properties, which might precipitate thromboembolic complications. The author has already found this to be the case with intravenous injections of cobra venom and of Congo red.[7]

The prediction mentioned has been brilliantly confirmed by the report made in 1945 by Moldavsky, Hasselbrock, Cateno, and Goodwin, who found that varying dosages of penicillin administered by both the oral and intramuscular routes, "produced a marked increase in the speed with which the blood clotted in human patients."[8]

For this reason, in the interest of preventive medicine and public health, the present writer wishes to announce his studies on another important group of drugs extensively employed in therapeutics. In the fall of 1943, experiments

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were begun on rabbits and cats, and to a lesser extent on dogs, concerning the thromboplastic properties of certain mercurial diuretics widely employed in cardiovascular practice. The three diuretics studied were Mercupurin, Salyrgan, and Mercuhydrin. Inasmuch as Mercupurin* and Salyrgan* are marketed in combination with theophylline, experiments were performed not only with such commercial solutions, but especially with solutions of the mercurials without theophylline.

It was found that all three of these mercury compounds, both by intramuscular injection and by injection into a vein, exerted a definite thromboplastic effect on the blood of rabbits and cats. Such an effect usually developed one to two hours after administration of the drugs but sometimes appeared much earlier. Numerous control experiments with other drugs, including caffeine, diuretin, theophylline, aminophylline, and sulfadiazine, did not indicate that these drugs produced an increase in the speed of clotting. Penicillin was used in control experiments and produced a marked thromboplastic effect, thus corroborating the findings of Moldavsky and his co-workers.

Eighty experiments on rabbits, and thirty-five on cats have already been performed in studying the thromboplastic property of mercurials. The following protocols will serve as illustrations of the results which will be published in detail later.

On June 27, 1945, a brown rabbit weighing 2,000 grams received 10 mg. of Mercupurin intravenously. The coagulation time before injection of the mercurial was 7 minutes. One hour after injection of the mercurial, the coagulation time was 4 minutes. Three hours after the injection the coagulation time was 3½ minutes.

On June 27, 1945, a white rabbit weighing 2,000 grams was given 10 mg. of Salyrgan into an ear vein. The coagulation time before the mercurial was injected was 12 minutes. One hour after injection the coagulation time was 4½ minutes. Two and one-half hours after the injection of the mercurial, the coagulation time was 4 minutes.

On June 1, 1945, a grey rabbit weighing 1,800 grams received 0.5 c.c. of Mercuhydrin solution intravenously. The coagulation time before injection was 7 minutes. Forty minutes after injection the coagulation time was 1½ minutes. One and one-half hours after injection, the coagulation time was 2½ minutes. Three hours after injection the coagulation time was 3½ minutes.

On June 11, 1945, a white rabbit weighing 2,200 grams received 20 mg. of Mercupurin intramuscularly. The coagulation time before the injection was found to be 9½ minutes by seven determinations on two successive days. Two hours after the mercurial was injected the coagulation time was 3½ minutes.

On June 11, 1945, a grey rabbit weighing 2,100 grams was given 20 mg. of Salyrgan intramuscularly. Seven determinations on two successive days showed the coagulation time to be 7½ minutes before the mercurial was administered. Two hours after the mercurial the coagulation time was 1½ minutes. Three hours after injection the coagulation time was 4 minutes. On the following day, the coagulation time was 7 minutes.

On June 15, 1945, a grey rabbit, weighing 2,000 grams received 10 mg. of Mercuhydrin intramuscularly. The coagulation time before the injection was 7 minutes. Thirty minutes after the injection the coagulation time was still 7 minutes. Three hours after the injection the coagulation time was 2½ minutes.

On June 8, 1945, a small cat weighing 1,000 grams was anesthetized with Nembutal and given Mercupurin intramuscularly. The coagulation time before the injection of the

*These preparations were furnished through the courtesy of the manufacturers, The Campbell Products, Inc., supplying Mercupurin and The Winthrop Chemical Co., Inc., Salyrgan.

mercurial was 13 minutes. Twenty-four minutes after the injection, the coagulation time was 12 minutes. One hour after the injection, the coagulation time was 1 minute. One and one-half hours after the injection of mercurial the coagulation time was 2½ minutes. Three hours after the injection the coagulation time was 4 minutes.

On June 8, 1945, a small cat, weighing 900 grams, received 10 mg. of Salyrgan intramuscularly. The coagulation times were 6½ minutes before injection; 1 minute, fifty-five minutes after injection; and 2 minutes, 45 seconds, two hours after the injection.

On June 1, 1945, a rabbit weighing 2,000 grams was used as a control. It received 10 mg. of theophylline intravenously. The coagulation times were 11½ minutes before the injection; 10½ minutes, one hour after the injection; 11 minutes, two hours after injection; 11 minutes, three hours after injection; and 12 minutes, three and one-half hours after injection.

COMMENT

In the present paper the results obtained with the clotting of whole blood only are reported. The phenomenon of clotting is, of course, a very complex one. The exact mechanism in any given case involves a study of platelets and determinations of prothrombin, of calcium, of fibrinogen, of antibodies, and of those other clotting factors in the blood which, as Theis[9] put it, "as yet, cannot be effectively measured." Such studies are now in progress and will be reported. It may be added that the three mercurial diuretics which we particularly studied were not the only ones which increased the speed of clotting; a number of other mercury compounds also exhibited this property.

Sudden death from mercurial diuretics has been repeatedly described and a valuable symposium on the subject was published in 1942.[10-14] Most recently, Volini and his co-workers[15] discussed various explanations for these sudden deaths and in their paper announced for the first time some of the results of the author's experiments with these drugs which he had given to them in June, 1944, in a personal communication.

The reported fatalities and toxic reactions should not discourage the rational use of mercurial diuretics. They should, however, serve as a warning of what can be expected in rare instances, particularly when such agents are used promiscuously.

It is a pharmacologic truism that every drug is a poison and, conversely, almost every poison may have a medicinal or therapeutic value.[16] The more we investigate the various factors which determine the difference between "poison" and "therapeutic agent," the greater the benefit to public health.

Thus it is quite logical for the pharmacotherapist, after the discovery of the thromboplastic properties of mercurial diuretics, to turn his attention to other pharmacologic agents which might counteract this undesirable effect without interfering with the useful diuretic properties of these compounds. Such studies are now in progress. Complete physiologic, pharmacologic, and other experimental data will appear in the *Archives Internationales de Pharmacodynamie et de Therapie*.

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AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

II. The Duration of the T-P Interval and Its Relationship to the Cycle Length (R-R Interval)

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THE period of electrical inactivity of the heart as recorded in the electrocardiogram by the T-P interval never attracted much attention. In going through the literature, one is struck by the paucity of material on this topic. Lombard and Cope,[1] in 1919, measured the cardiac diastole and systole with mechanical devices and noted that there was a shortening of diastole with increase in heart rate. They also mentioned the fact that diastole shortens much more rapidly than systole. Ashman and Hull[2] mention the fact that the T-P interval shortens with increase in heart rate and with prolongation of the P-R interval.

As long as the P-R, QRS, and S-T measurements fall within certain limits, they are considered to be normal, according to present criteria. These limits, we know, are quite wide, and suggestions are constantly being made to extend them just a little bit further. Yet it is felt that, in some instances, there are disturbances of cardiac conduction, despite the fact that the P-R, QRS, etc., are at or within the upper limits of normal. At constant cycle lengths, prolongation of the P-R, QRS, and S-T intervals produces a compensatory shortening of the T-P interval. The change in the T-P interval, therefore, should be relatively great because it represents the sum of all the prolongations in the various other components of the cycle. It was decided to determine if a constant relationship between the T-P interval and cardiac cycle length (C) existed. If such a relationship existed, perhaps it could be used in recognizing conduction disturbances early. Before this could be pursued any further, it was necessary to determine the following: (1) Is there a constant, predictable relationship between T-P and C in normal individuals? (2) If such a relationship, or correlation, does exist, how predictable is it? (3) What kind of relationship is it and how can it be expressed? (4) How great is the normal scatter? (5) How does physiologic tachycardia, e.g., the tachycardia produced by exercise, affect this relationship?

METHOD

The procedure in this work was outlined in the first paper of this series.[3] The same electrocardiograms were used in both studies. The T-P interval was measured from the end of the T wave (where the T wave returns to the isoelectric line and remains there) to the beginning of the following P wave. In Table I is listed the age distribution of the 495 cases in the series.

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TABLE I. AGE DISTRIBUTION OF TOTAL NUMBER OF CASES

AGE (YRS.)	NO.	AGE (YRS.)	NO.	AGE (YRS.)	NO.
18	19	26	22	34	5
19	60	27	15	35	8
20	50	28	10	36	8
21	63	29	14	37	11
22	42	30	17	38	7
23	37	31	11	39	2
24	38	32	10	42	3
25	32	33	10	44	1
				Total	495

RESULTS AND DISCUSSION

A scatter diagram (Fig. 1) was constructed, plotting the T-P interval against the C measurements in all 1,419 readings. On inspection, there appears to be a definite and constant relationship between the two variables. To determine how great this correlation is, the following was done. Two curves were constructed (Figs. 2 and 3): one shows the average T-P measurement for each C value (Fig. 2), thus making C the independent variable; and the other (Fig. 3), shows the average C reading for each T-P value, making T-P the independent variable. Upon superimposing the two curves (Fig. 4), it is seen that the two variables depend on each other very closely. The correlation is greatest for the C values from 0.465 second to 0.751 second (heart rates about 130-80 per minute), where 70.3 per cent of the cases fall; and for the T-P values 0.071 second to 0.291 second, where 77.6 per cent of the measurements fall. The limits, which correspond to the intersection of the means plus and minus the standard deviation of C and T-P, respectively, are shown by the box drawn in Fig. 4. This area includes 66.1 per cent of all the measurements. The degree of correlation expressed by the coefficient of correlation[4-6] was calculated (Fig. 5) and found to be plus 0.986; a value of 1.000 representing perfect correlation, and a value of 0.000 representing no correlation. Therefore, this can be considered indicative of a very high positive correlation. Gross inspection and testing by Fisher's method of analysis of variance[4] showed that the T-P to C relationship is linear. The few measurements that deviate from the curve are probably due to random sampling. Having determined that the relationship of the two variables is linear, the equation for the straight line curve was calculated. Fig. 6 shows the determination of the slope,[4-6] and in Fig. 7, *A*, the close agreement between the actual data and the calculated straight line curve is illustrated. Thus the relationship of T-P to C can be expressed:

$$\text{T-P} = 0.737\ \text{C} - 0.267.$$

The standard error for the prediction of T-P in this equation was found to be 0.026. The preceding can also be expressed:

$$\text{K} = \frac{\text{T-P} + 0.267}{\text{C}},$$

where K is a constant whose value is 0.737 with a standard deviation of 0.048.

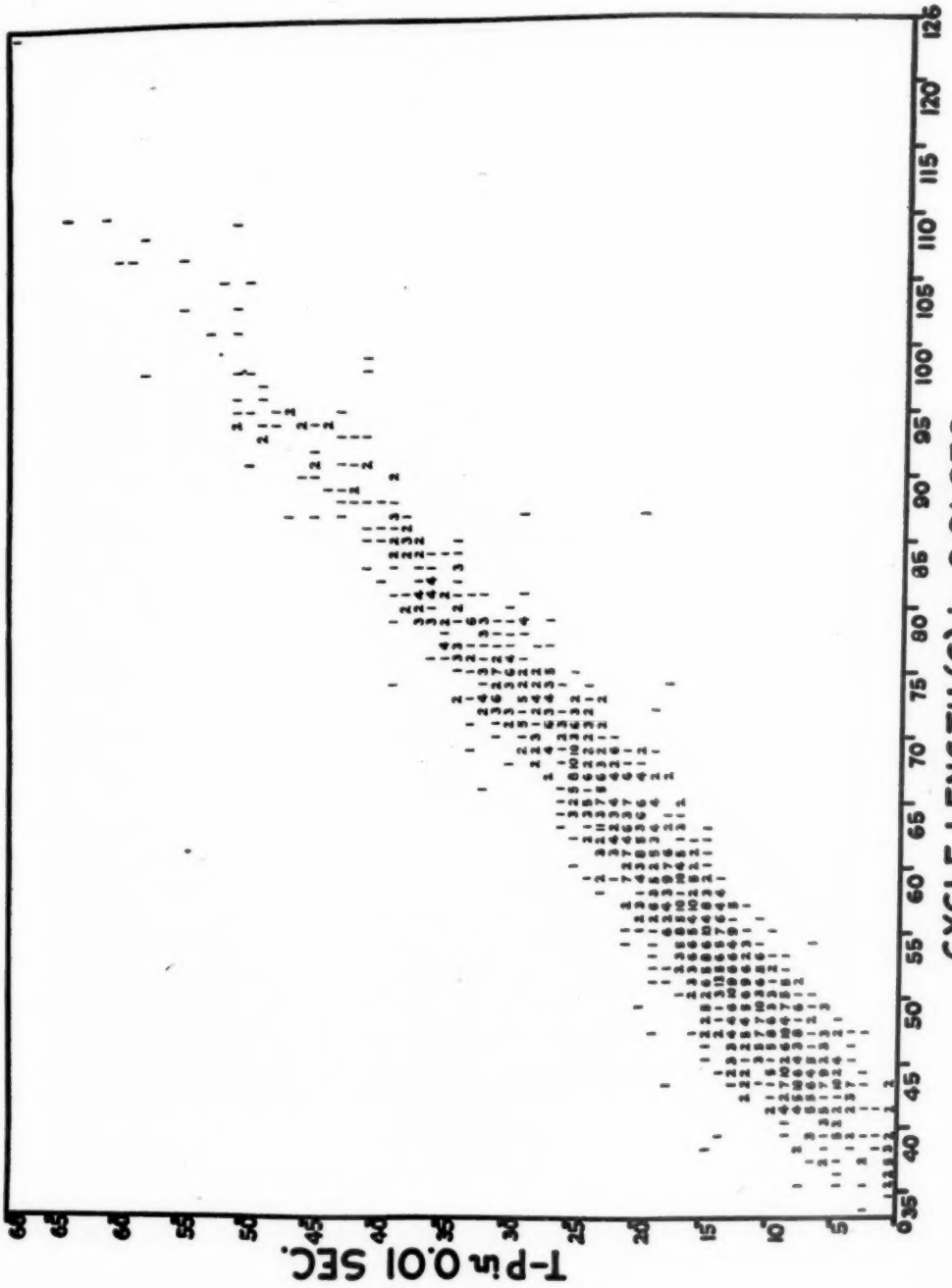


Fig. 1.—Scatter diagram of total readings before and after exercise.

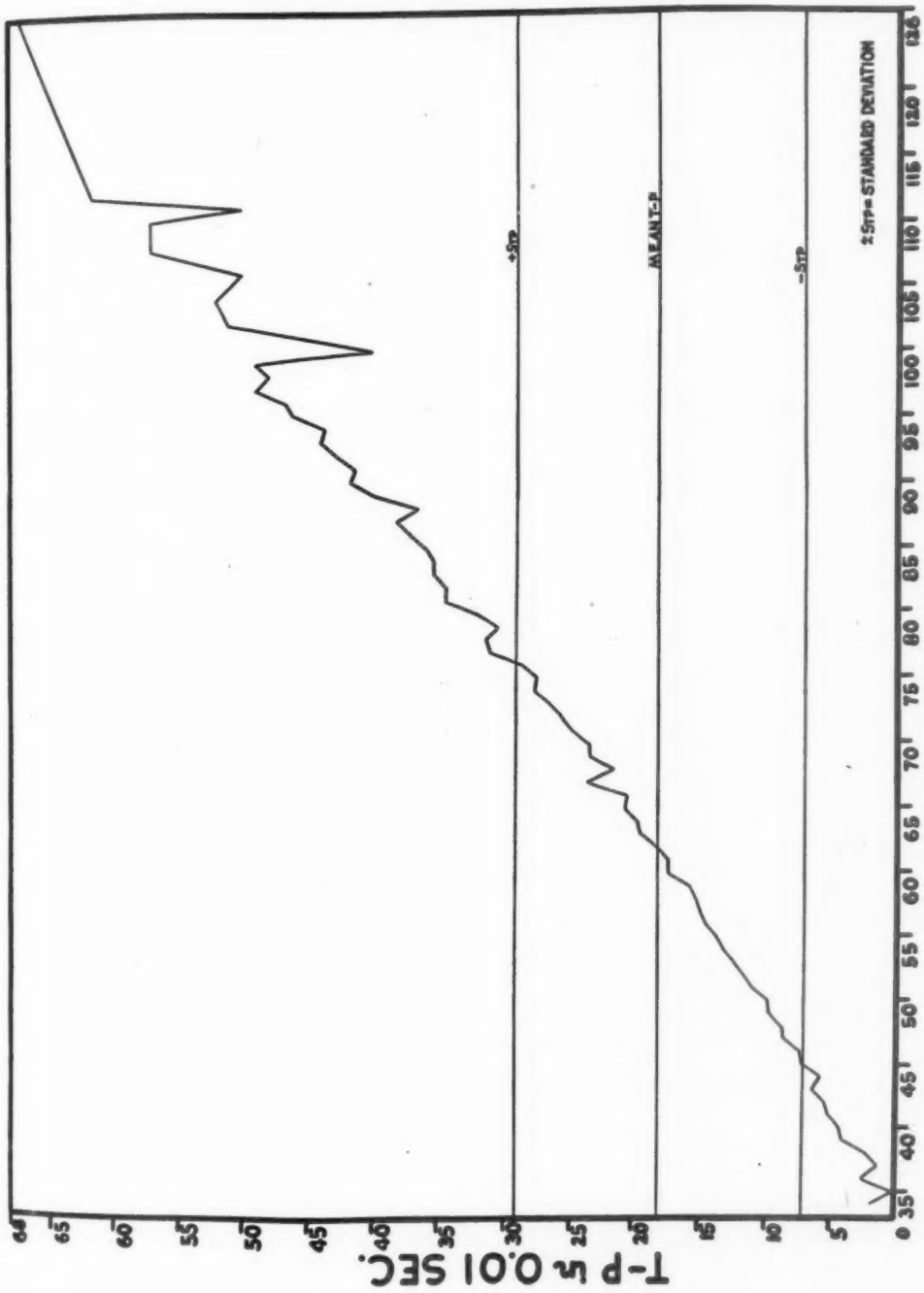


Fig. 2.—Curve showing effect of change in C upon T-P in total readings before and after exercise.

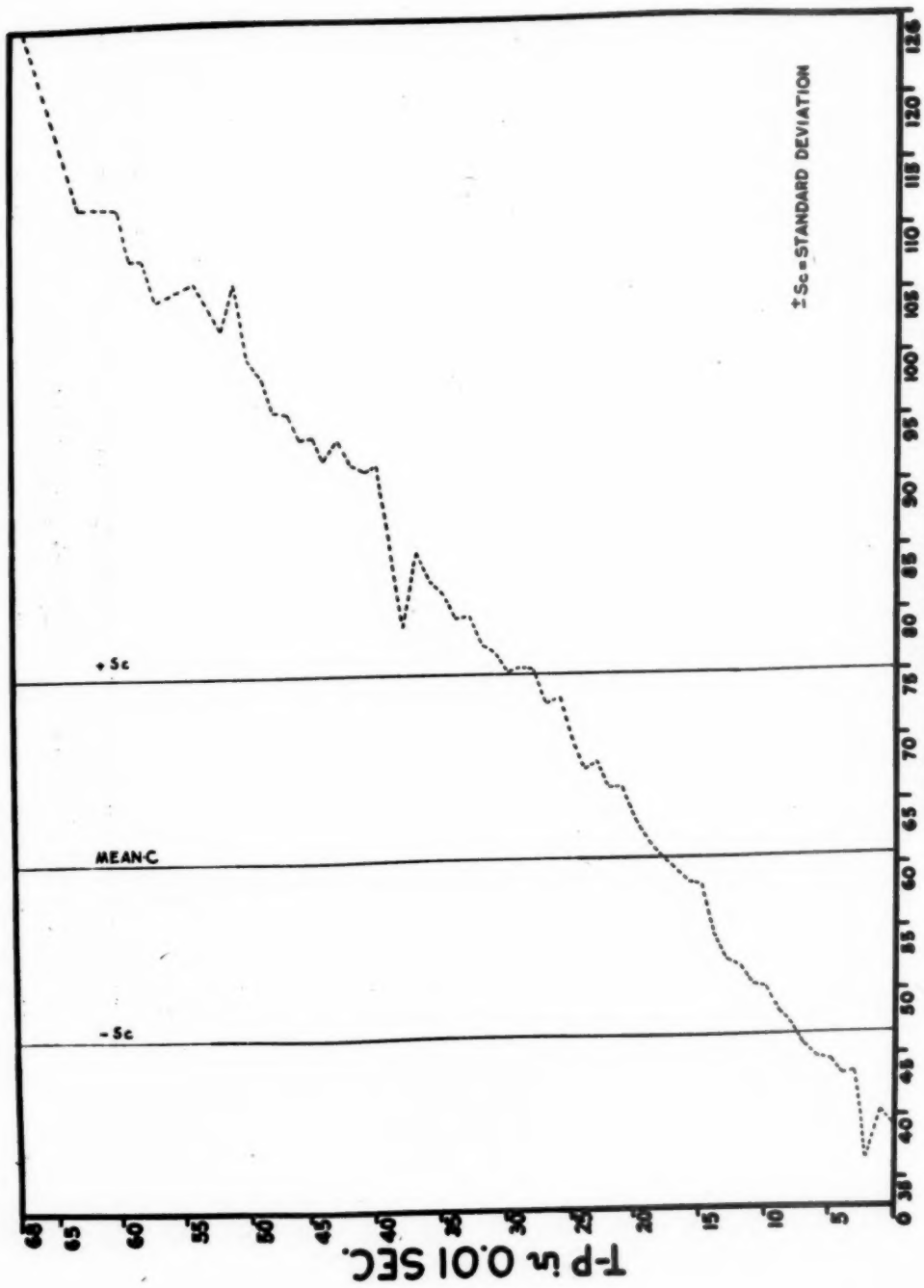


Fig. 3.—Curve showing effect of change in T-P upon C in total readings before and after exercise.

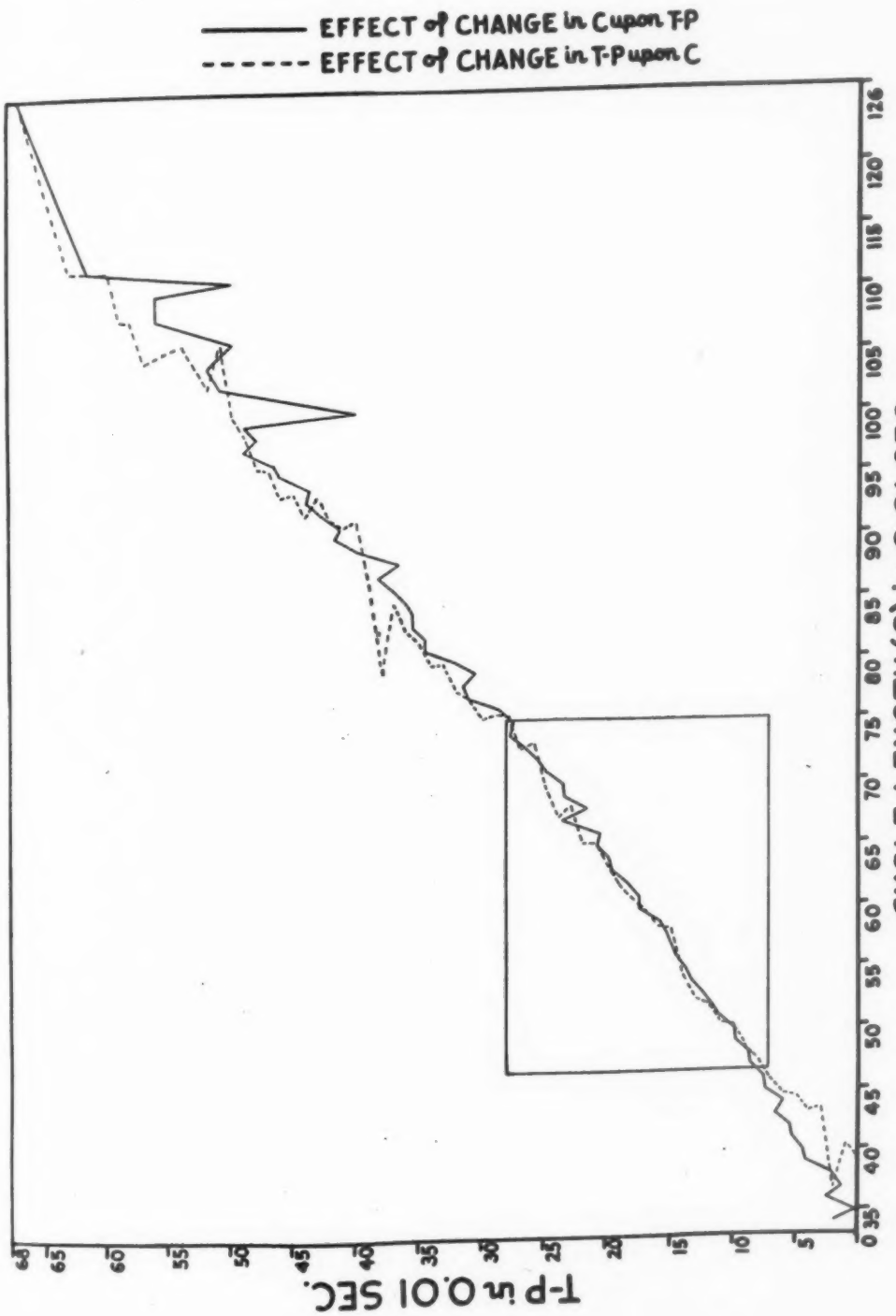


Fig. 4.—Composite curves—total readings before and after exercise.

Fig. 3.—Curve showing effect of change in T-P upon C in total readings before and after exercise.

$$r = \frac{\Sigma XY - \frac{(\Sigma X)(\Sigma Y)}{N}}{\sqrt{\Sigma X^2 - \frac{(\Sigma X)^2}{N}}\sqrt{\Sigma Y^2 - \frac{(\Sigma Y)^2}{N}}}$$

r = Coefficient
X = C in 0.01 Sec.
Y = TP in 0.01 Sec.
N = # Readings
Σ = Sum of

1. Total Readings Before & After Exercise

$$r = \frac{21.552}{21.848} = +0.986$$

Fig. 5.—Determination of coefficients of correlation for variables T-P and C.

TABLE II. DISTRIBUTION OF K VALUES IN 1,419 MEASUREMENTS

K	NO.	K	NO.	K	NO.	K	NO.	K	NO.
0.519	1	0.681	9	0.724	25	0.768	16	0.815	1
0.557	1	0.682	1	0.725	2	0.769	5	0.816	3
0.583	1	0.683	2	0.726	24	0.770	6	0.818	5
0.595	1	0.684	6	0.727	16	0.771	7	0.820	1
0.599	1	0.685	12	0.728	12	0.772	16	0.823	4
0.607	2	0.686	10	0.729	10	0.773	10	0.825	1
0.608	2	0.687	2	0.730	21	0.774	14	0.826	1
0.613	1	0.688	2	0.731	5	0.775	4	0.827	4
0.620	1	0.689	6	0.732	10	0.776	6	0.828	4
0.621	1	0.690	9	0.733	13	0.777	11	0.830	2
0.627	1	0.691	11	0.734	21	0.778	13	0.831	4
0.632	1	0.692	10	0.735	14	0.779	4	0.834	2
0.634	3	0.693	11	0.736	11	0.780	13	0.836	2
0.636	1	0.694	8	0.737	30	0.781	13	0.838	4
0.637	2	0.695	10	0.738	12	0.783	7	0.841	1
0.638	3	0.696	7	0.739	6	0.784	6	0.842	3
0.640	2	0.697	1	0.740	9	0.785	6	0.844	2
0.642	3	0.698	14	0.741	16	0.786	11	0.846	1
0.643	2	0.699	2	0.742	2	0.787	3	0.847	1
0.646	4	0.700	9	0.743	11	0.788	3	0.849	2
0.649	2	0.701	4	0.744	7	0.789	13	0.850	1
0.651	1	0.702	9	0.745	37	0.790	5	0.851	2
0.652	3	0.703	17	0.746	10	0.791	6	0.857	2
0.654	1	0.704	16	0.747	4	0.793	3	0.860	1
0.655	1	0.705	16	0.749	27	0.794	7	0.861	1
0.657	4	0.706	11	0.750	10	0.795	3	0.862	1
0.658	2	0.707	9	0.752	13	0.796	1	0.863	1
0.659	1	0.708	7	0.753	6	0.798	5	0.864	2
0.661	5	0.709	8	0.754	24	0.799	4	0.866	1
0.662	4	0.710	6	0.755	5	0.801	3	0.870	1
0.663	1	0.711	12	0.756	16	0.802	6	0.878	2
0.667	9	0.712	20	0.757	6	0.803	1	0.880	1
0.668	16	0.714	16	0.758	5	0.804	4	0.883	1
0.671	4	0.715	2	0.759	26	0.805	1	0.885	1
0.672	2	0.716	10	0.760	6	0.806	4	0.914	1
0.673	8	0.717	16	0.761	16	0.807	9	0.932	1
0.674	12	0.718	4	0.762	11	0.808	3	0.936	1
0.675	8	0.719	5	0.763	14	0.809	2	0.968	1
0.677	7	0.720	17	0.764	15	0.810	1	0.993	2
0.678	3	0.721	12	0.765	18	0.812	3	1.044	1
0.679	1	0.722	17	0.766	20	0.813	2		
0.680	6	0.723	1	0.767	3	0.814	5		

$K = \frac{T\text{-}P + 0.267}{C}$; S.D. = Standard deviation = 0.048
K = 0.737

0.737± S.D. includes 74.6 per cent of all measurements.
0.737± 2 S.D. includes 95.2 per cent of all measurements.
0.737± 3 S.D. includes 99.2 per cent of all measurements.

$$K_3 = \frac{\Sigma XY - \frac{(\Sigma X)(\Sigma Y)}{N}}{\Sigma X^2 - \frac{(\Sigma X)^2}{N}}$$

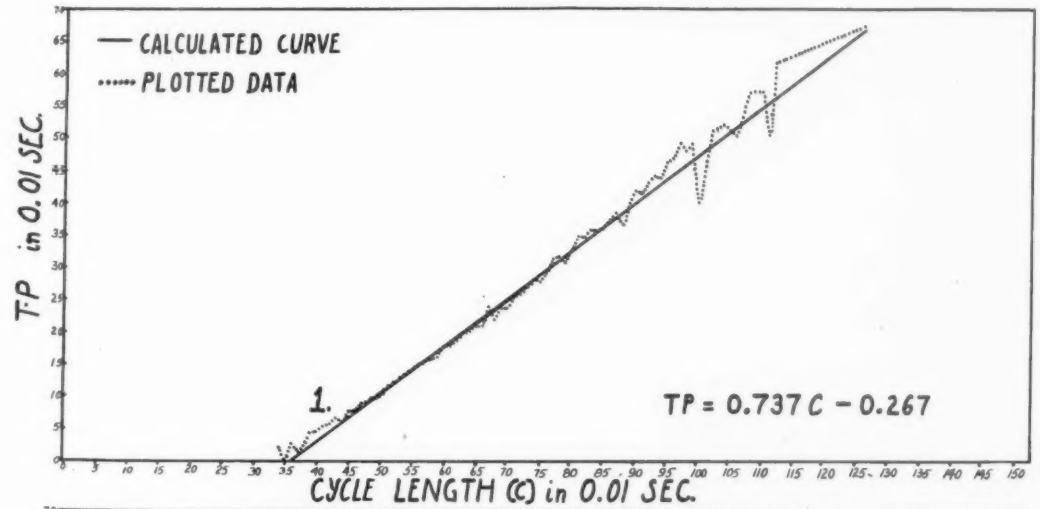
K_3 = Slope
X = C in 0.01 sec.
Y = TP in 0.01 sec.
N = # Readings
Σ = Sum of

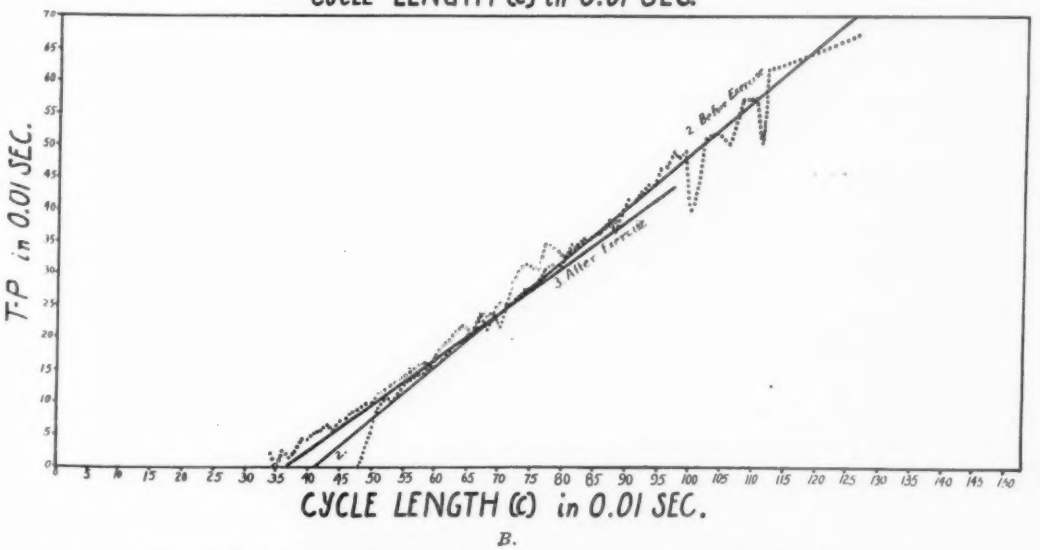
1. Total Reading Before & After Exercise

$$K_3 = \frac{21.552}{29.224} = +0.737$$

Fig. 6.—Determination of slopes of curves for T-P and C relationship.

A.





B.

Fig. 7.—Relationship of calculated to plotted curves. *1*, Total readings before and after exercise; *2*, before exercise; *3*, after exercise.

Table II shows the range and distribution of K values found in all 1,419 measurements. The scatter is not great, for K plus and minus twice the standard deviation includes 95.2 per cent of all the readings. The percentage of readings that falls outside the limits set by K plus and minus three times the standard deviation, beyond which the deviation is considered significant, is small enough (12 measurements) to be considered as due to the error inherent in this study.

The data collected before and after exercise were analyzed in the same fashion as the total number of measurements. It was found that exercise did not cause any significant change in the T-P to C relationship. Fig. 7, *B*, illustrates the actual data and the calculated curves, both before and after exercise.

As mentioned in the previous paper,[3] the curve and equation arrived at as a result of this investigation, represents the composite of all the curves derived from the measurements of the electrocardiograms of many individuals. Therefore, in its application to the individual case, variations should be expected. It was found that these remain within the range of values that comprise the normal scatter. When the measurements in the individual subject made at different cycle lengths are plotted, the resulting curve approximates the composite curve in type, and the deviation remains within the normal limits.

The effect of various factors, e.g., carditis, cardiac hypertrophy, drugs, and coronary sclerosis, were not included in this study. Therefore, it cannot be predicted at this time whether the T-P to C relationship and the equation derived for it, will be of any value in studying cardiac disturbances.

CONCLUSIONS

1. In normal young men, there is a constant relationship, with a significant positive correlation, between the T-P interval and the cycle length.

2. This relationship is linear and can be expressed by the equation:

$$\text{T-P} = 0.737\ \text{C} - 0.267$$

or

$$\text{K} = \frac{\text{T-P} + 0.267}{\text{C}},$$

where K is a constant (0.737) with a standard deviation of 0.048.

3. Tachycardia produced by exercise in normal young men does not alter the relationship.

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AN ANALYSIS OF THE TIME RELATIONSHIPS WITHIN THE CARDIAC CYCLE IN ELECTROCARDIOGRAMS OF NORMAL MEN

III. The Duration of the P-R Interval and Its Relationship to the Cycle Length (R-R Interval)

Captain Isadore Schlamowitz, M.C.
Army of the United States

THE P-R interval, or that portion of the electrocardiogram which records the electrical innervation of the auricles and the time of conduction of the electrical impulses across the auriculo-ventricular groove, has been of interest for many reasons. Most of the work on this subject has consisted of attempts to ascertain the "normal" duration, of the P-R interval and its various deviations from the "normal" which disease or other factors produce. However, some investigators have attempted to determine whether or not there was any relationship between the cardiac cycle length and the length of the P-R interval.

After reviewing the literature on this subject, one is left undecided as to whether or not there is any constant relationship between the P-R interval and the cycle length, for the different authors contradict each other. Bazett,[1] in 1920, found that in his series the P-R interval was closely related to the cycle length (R-R). He expressed the relationship by the formula: $P\text{-}R = 0.06 - 0.10\sqrt{C}$, where C is the cycle length in seconds. The readings, however, deviated quite a little from the predicted curve, and Bazett explained this as being due to factors such as fatigue. Pardee[2] states that the P-R interval shortens with increases in the heart rate. However, he does not propose any formula to express this relationship, nor does he describe, just how close this relationship is.

Since then this subject has been investigated by other workers with varying results. One group [4, 5, 9, 10] found that the P-R interval becomes shorter with increase in the heart rate, but no formulas were proposed to express this relationship. Scheer and Albers,[6, 7] however, found that not only was there a constant relationship between the P-R interval and C, but they also proposed a formula to express this relationship. Their equation is: $P\text{-}Q = 1.73\sqrt{C}$. It is notable that all equations thus far proposed indicate that the P-R interval—cycle length relationship is curvilinear. In 1936, Shipley and Hallaran[3] and, in 1940, Benedetti[8] found that, in their series, they could not find a constant relationship between the P-R interval and the cycle length.

It was therefore decided to study this subject in a large series of normal individuals to determine the following, if possible: (1) Is there a constant, predictable relationship between P-R and C in normal individuals? (2) If such a relationship, or correlation, does exist, how predictable is it? (3) What kind of relationship is it and how can it be expressed? (4) How great is the normal

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SCATTER DIAGRAM SHOWING DISTRIBUTION OF TOTAL READINGS
BEFORE AND AFTER EXERCISE

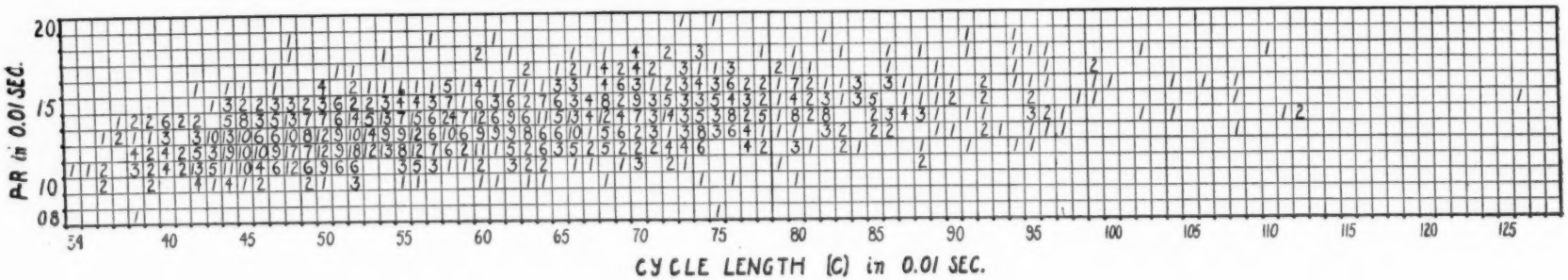

Fig. 1.

scatter? (5) How does physiologic tachycardia, e.g., the tachycardia following exercise, affect this relationship?

METHOD

The procedure in this work was outlined in the first two papers of this series.[11, 12] The same electrocardiograms were used in all three studies. The P-R interval was measured from the beginning of the P wave to the beginning of the first deflection of the QRS complex. The measurements were made in Lead II, since it was found that they could be made more accurately there than in any of the other leads. Furthermore, the length of the P-R measurements in Lead II were not exceeded in the other leads. In Table I is listed the age distribution of the 495 cases in this series.

RESULTS AND DISCUSSION

A scatter diagram (Fig. 1) was constructed, plotting the P-R interval against the C measurements in all 1,419 readings. On inspection, there does not appear to be a constant relationship between the two variables, although there does appear to be a slight tendency for the P-R intervals to be a little shorter at the shorter cycle lengths. To analyze this data objectively, it was decided to determine the coefficient of correlation.[13-15] This was found to be plus 0.387; a value of 1.000 representing perfect correlation, and a value of 0.000 representing no correlation. This is indicative of a positive but very low correlation. Statistically, it is not considered significant. It was also found that after exercise the degree of correlation was less than before exercise. That is, the scatter of values became much greater after exercise than before. The coefficients of correlation for before and after exercise were: before exercise, plus 0.440; after exercise, plus 0.195.

TABLE I. AGE DISTRIBUTION OF TOTAL NUMBER OF CASES

AGE (YRS.)	NO.	AGE (YRS.)	NO.	AGE (YRS.)	NO.
18	19	26	22	34	5
19	60	27	15	35	8
20	50	28	10	36	8
21	63	29	14	37	11
22	42	30	17	38	7
23	37	31	11	39	2
24	38	32	10	42	3
25	32	33	10	44	1
			Total		495

It was then decided to determine whether there was any significant difference between the P-R values before and after exercise. The mean values of the P-R intervals and the standard deviations for before and after exercise are shown in Table II.

It is seen that although there appears to be a tendency for the P-R interval after exercise to be shorter, the difference is more apparent than real. For the P-R values after exercise to be significantly different from those found before exercise, a difference greater than three times the standard deviation should

TABLE II. THE MEAN VALUES OF THE P-R INTERVALS AND THE STANDARD DEVIATIONS BEFORE AND AFTER EXERCISE

	MEAN P-R	STANDARD DEVIATION
Before exercise	0.143 second	0.014
After exercise	0.129 second	0.010
Total readings	0.135 second	0.017

be present. In this series the difference was less than even twice the standard deviation.

In examining Fig. 1 it will be seen that in this series of 1,419 measurements in normal individuals the range of P-R values was from 0.08 to 0.20 second. There were no instances found where the P-R interval fell beyond these values. A check through the records of all cases not used in this study also failed to reveal any instance of a P-R interval prolonged beyond 0.20 second.

Since there is no significantly constant relationship between the P-R interval and the cycle length, this could not be used for the purpose of studying the activity of the conduction system.

CONCLUSIONS

1. In normal young men, there is no significantly constant relationship or correlation between the P-R interval and the cycle length.

2. The duration of the P-R interval before exercise is not significantly different from the values found after exercise.

3. In no case was the P-R interval found to exceed 0.20 second.

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THE EFFECT OF CHANGE OF POSITION OF THE ARM UPON BLOOD PRESSURE

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IF ONE looks at an anatomic sketch of the vascular tree, the blood channels from the heart to the arm are in the shape of a hairpin when this limb is held at the side of the body. When the arm is abducted 90 degrees from the side, the hairpin curve is eliminated and the vessels are more or less at a right angle. When the arm is hyperabducted* 180 degrees, the subclavian, axillary, and brachial arteries are in a fairly straight line. Theoretically speaking, the more direct the pathway, the less is the pressure head of the blood column diminished in overcoming the resistance of a circuitous route. If this assumption is correct, blood pressure should be lowest when the arm is in the first position, intermediate in the second, and highest in the last. This conception might also help to explain the marked difference in pressure between the upper and lower extremities, as the path in the latter is much more direct. Such a pressure gradient has been the subject of much speculation and study in the past.

PROCEDURE

With these considerations in mind, it was thought that, if the patient were stabilized in the supine position and the effect of gravity eliminated by moving the arm into a horizontal plane at the level of the heart, the changes in blood pressure under basal conditions could be due only to alteration in directness of or anatomic interference with the blood flow.

One hundred young adults between the ages of 20 and 35 years were examined in the order of their hospital admission. All of them were well except for trench foot, which was the cause of their hospitalization.

After a blood pressure cuff of standard width (14 cm.) had been snugly fitted above the left elbow, the patients rested on their backs for fifteen minutes. The first fifty patients kept the left arm close to the side; in the second group of fifty patients blood pressures were first taken with the arm hyperabducted. Systolic and diastolic readings were made by the auscultatory method and according to the usual criteria.[1] In order to further minimize experimental errors due to activity of internal organs, emotion, and other nervous influences, the readings were taken approximately three hours after breakfast, by the author, who knew the patients and had taken their blood pressure on other occasions. After a preliminary determination of the approximate levels two readings were taken in succession, and the average was recorded. Such readings were either identical or differed from each other by no more than 2 millimeters. The same Baumanometer, correctly calibrated, was used to take all the readings. For the second reading the arm was moved into the position of hyperabduction by the first fifty patients, and adducted directly to the side by the other fifty patients. After waiting two minutes, readings were taken again with the bell of the stethoscope in the same location as for the initial readings. The blood pressure varied uniformly in the

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*The term *hyperabduction* is not, strictly speaking, a suitable one because the arm is in the midline at its terminal phase. In this article, it will be used to denote the position in which the entire upper extremity is in a line with the long axis of the body, whether the patient is sitting, standing, or lying.

same direction, regardless of whether the arm was first held against the side or in the position of hyperabduction. In twenty patients an intermediate position, with the arm at right angles to the body, was also tried. Readings taken in an intermediate position were illustrative of the general trend but added no special information except in the patients with elevated blood pressure.

RESULTS

Although the readings varied appreciably with change in position of the arm, the direction of change was the reverse of that we had expected: that is, the blood pressure was uniformly higher with the arm at the side than with the arm hyperabducted. The diastolic pressure remained remarkably constant, but the systolic pressure varied from an average of 15 mm. to as much as 20 to 30 millimeters. In one individual when the arm was hyperabducted there was complete absence of pulse.

Twenty-nine patients showed no significant change in systolic or diastolic values. The readings of the remaining 71 patients, expressed in average values, are shown in Table I.

TABLE I. THE INFLUENCE OF THE POSITION OF THE ARM ON THE AVERAGE VALUES OF THE BLOOD PRESSURE IN SEVENTY-ONE PATIENTS WITH NORMAL PRESSURE

POSITION OF ARM	AVERAGE BLOOD PRESSURE (MM. HG)		
	SYSTOLIC	DIASTOLIC	PULSE PRESSURE
Arm at side	132	77	55
Arm hyperabducted	117	76	41

These differences in blood pressure are obviously not due to the effect of gravity or of engorgement of the venous reservoir.

In patients with significant change in blood pressure there was a diminution in intensity of the auscultatory phases, sometimes so marked that the diastolic pressure was difficult to ascertain. There was no change in pulse rate in the different positions.

An analysis of the six patients whose blood pressures were abnormal in one of the three standard test positions is shown in Table II.

In five of these cases, the blood pressure with the arm in a neutral position was normal.

TABLE II. EFFECT OF CHANGING THE POSITION OF THE ARM IN SIX PATIENTS WITH SLIGHT HYPERTENSION

CASE	BLOOD PRESSURE (MM. HG)		
	ARM AT SIDE	ARM AT RIGHT ANGLE TO LONG AXIS OF BODY	ARM HYPERABDUCTED
1	150/82	138/84	126/86
2	158/104	148/104	148/102
3	160/86	146/86	136/84
4	152/76	146/76	138/78
5	154/80	140/84	130/84
6	152/94	144/94	136/92

DISCUSSION

Accuracy in determining the blood pressure requires the avoidance of common errors. This is especially true with regard to the position of both

the patient and the extremity. It is advocated both in this country and abroad that the "patient should be comfortably seated with the arms slightly flexed and the whole forearm supported at heart level on a smooth surface."[1] The supine position can be interchanged with the sitting position, provided notation is made of the fact, since there is no significant difference in blood pressure readings made in the sitting and lying positions.

In the accepted criteria for measuring blood pressure, there is no reference to the position of the arm or the distance it should be held from the side of the body, although it is specified that "there should be no constriction of the arm due to clothes or other objects."[1] It is well known, however, that if the arm is brought too close to the chest wall, external pressure by the latter on the cuff may lead to gross inaccuracies in the reading. Unfortunately, many blood pressure readings are still taken in just this manner.

Other investigators have considered the effect of the position of the arm on hydrostatic pressure and venous engorgement.[2, 3] Our figures prove quite conclusively that marked deviations of the arm from a neutral, relaxed position away from the side of the body produce appreciable differences in the blood pressure, even though the arm is maintained at the level of the heart. With the arm at the side (0°), the pressures tend to be high; with the arm hyperabducted (180°), they tend to be low.

In six of our subjects, when the arm was placed directly at the side of the body, the systolic pressure was definitely elevated. In five instances, when the arm was abducted, such high readings fell into the normal range. Although extremes of both positions are abnormal, the fact that the pressures were normal in the neutral position is of clinical significance and indicates the importance of rigid adherence to the rules laid down for blood pressure determination.

An interesting phenomenon observed in this study was the lowered blood pressure, and the weakened, and, in rare instances, absent pulse, when the arm was hyperabducted. In a recent article,[4] Wright demonstrated that when the arm was hyperabducted, the cords of the brachial plexus and the vascular structures to the arm were stretched under the coracoid process and compressed between the clavicle and the first rib or between the scalenus anticus muscle and the cervical transverse processes. Obliteration of the arterial pulse and numbness and tingling, the neurovascular symptoms of the *hyperabduction syndrome*, could be reproduced in such a high percentage of patients that they were not considered to be abnormal. We believe that these anatomic changes described by Wright[4] are the cause of the variation in blood pressure levels which occur when the position of the arm is changed. We did not find obliteration of the pulse as frequently as Wright, probably because we did not use such adjuvant measures as movement of the head, depression of the shoulder, and pronation and supination of the arm. The difference in the position of the patient may also have had some influence. Wright's patients were examined in the sitting position; ours were examined in the supine position.

Our findings re-emphasize the importance of using a standard position in taking blood pressures. Even minor changes of position, in many indi-

viduals, may result in false readings, which may even be pathologically high or low. Such false readings are sometimes inevitable, as when an anesthetist is forced to take blood pressure readings with the arm in positions demanded by the operation but not suitable for taking blood pressure estimations. The writer recalls a neurosurgical operation during which the anesthetist was extremely concerned throughout the operation over a blood pressure of 70/40, although the patient was in excellent condition and showed no signs of going into shock. The blood pressure was being taken with the arm in the position of hyperabduction.

SUMMARY

Position of the arm has a definite and uniform effect on blood pressure readings. The systolic pressure is lowest when the arm is hyperabducted, that is, when it is made to lie along the long axis of the body. The systolic pressure becomes higher as the arm is adducted and brought toward the side of the body in the horizontal plane. A neutral position of the arm, 45 to 90 degrees from the side of the body, is probably the optimum position for the estimation of blood pressure. Other positions may cause a marked discrepancy in blood pressure readings.

Acknowledgment is made to Colonel Irving S. Wright for helpful criticism and suggestions.

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ELECTROCARDIOGRAPHIC CHANGES IN SCRUB TYPHUS FEVER

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SCRUB typhus, or tsutsugamushi fever, is an acute infectious disease characterized by an abrupt onset, a remittent fever lasting from two to four weeks and terminating by lysis, a maculopapular erythematous eruption that persists for eight to twelve days, and marked prostration. The etiological agent is the *Rickettsia orientalis,* and transmission is by a mite larva. Primary pathologic changes include a vasculitis and a perivasculitis involving the parenchyma of the various organs with a slight tendency to thrombus formation.

Abnormalities of the cardiovascular system are a frequent complication during the acute attack in many of the cases. There is a protracted duration of the convalescent period which is associated with symptoms of extreme physical weakness. In some patients, symptoms referable to the cardiovascular system persist. Because of this, a study of the electrocardiographic changes present during the convalescent stage of the disease was undertaken. The electrocardiograms upon which this study is based were taken from six to eight weeks after the onset of the illness. The diagnosis was confirmed in all cases by a typical clinical course and positive agglutination reactions against *Bacillus proteus OX* (Kingsbury strain).

The patients observed consisted of 78 adult men, 64 of whom were under 30 years of age; the other 14 were less than 40 years old. All were white, with the exception of one who was a Negro. None of the patients gave histories of previous heart disease or of rheumatic fever. The physical examination in all patients revealed no evidence of organic heart disease. The blood pressure was within normal limits. Electrocardiographic studies were made in all cases without regard for the presence or absence of symptoms. All tracings were taken in the recumbent position. Routinely, the three standard limb leads were used, and in 41 cases (52.5 per cent) an additional single precordial lead (IVF) was made.

The standards of normal which were used were those suggested by Katz.[1] (1) P waves were considered abnormal if their duration exceeded 0.11 second, if notching was easily discernible, and if all the waves in the limb leads were smaller than 0.5 millimeter. (2) Low voltage was considered to be present when the QRS complex measured 5 mm. or less in each of the limb leads or when the sum of the amplitude of the QRS complexes in all three leads was less than 15 millimeters. (3) Q and S waves were considered to be abnormal when these waves measured one-fourth or more of the amplitude of the R wave. (4) Devia-

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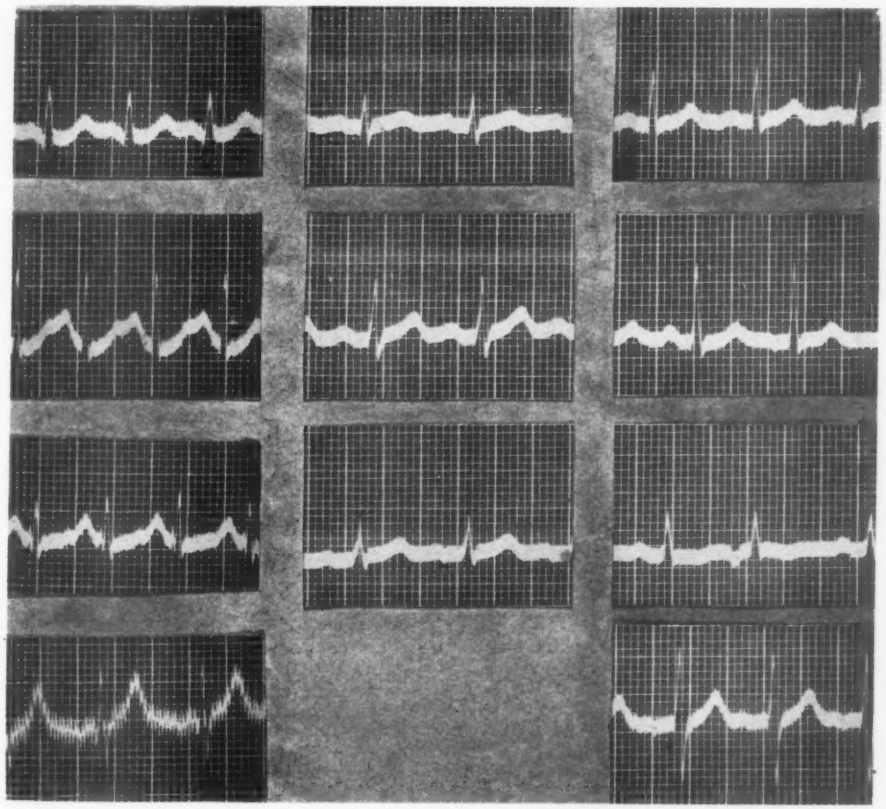
tions of the electrical axis to the left of over 35 degrees were regarded as abnormal. (5) The RS-T segments were considered to be depressed when there were deviations of more than 0.5 mm. in Leads I and II and 0.75 mm. in Lead III. The RS-T segments were considered to be elevated if the deviation was 1.5 mm. or more in the limb leads. (6) In all limb leads only T waves which were less than 1 mm. in amplitude were regarded as being low. Inverted T waves received consideration only when they occurred in Leads I or II. A definitely inverted T wave in the chest lead was regarded as an abnormality.

Symptoms.—Symptoms referable to the heart were present in 27 cases (34.6 per cent). These consisted of tachycardia, palpitation, dull pain in or over the heart, occasional breathlessness, and easy fatigue. Weakness was the only complaint in 12 patients (15.4 per cent). The remaining 39 patients (50 per cent) had no symptoms. Of the 27 patients with symptoms suggestive of cardiac disease, 20 had abnormal electrocardiographic patterns, while seven had tracings that were within normal limits. There were two patients with normal electrocardiograms and ten patients with abnormal patterns in the group of twelve patients whose only complaint was weakness. Of the 39 patients without symptoms, 13 gave normal tracings while 26 had some electrocardiographic abnormality. Five of the six patients who developed cardiac decompensation during the acute attack showed low amplitude of the QRS complex. Frequently changes in the electrocardiograms of patients without recognized heart disease were quite striking.

TABLE I. INCIDENCE (IN PER CENT) OF ELECTROCARDIOGRAPHIC CHANGES IN SEVENTY-EIGHT CASES OF CONVALESCENT SCRUB TYPHUS

ABNORMAL CHANGES	TOTAL INCIDENCE	ISOLATED FINDING	ASSOCIATED ECG ABNORMALITIES										PRESENCE OF SYMPTOMS REFERABLE TO HEART
			SINUS TACHYCARDIA	PROLONGED P WAVE DURATION	P-R INTERVAL AT UPPER LIMIT OF NORMAL	PRESENCE OF Q WAVES	DECREASED AMPLITUDE OF QRS	PRESENCE OF S WAVES	RS-T SEGMENT DEVIATIONS	T-WAVE CHANGES	PREMATURE CONTRACTIONS	LEFT AXIS DEVIATION	
Sinus tachycardia	46.1	4	–	20	18	9	9	20	15.6	13	2.6	4	20
Prolonged duration of the P wave	29.5	2.6	20	–	12	5.2	2.6	18	6.5	9	1.3	5.2	10.4
Presence of Q waves	12.8	–	9	5.2	4	–	–	4	8	4	–	1.3	4
Decreased amplitude of the QRS complex	12.8	–	9	2.6	1.3	–	–	4	2.6	–	1.3	–	8
S waves in two different limb leads	27	–	8	9	2.6	–	8	–	2.6	5.2	1.3	6.5	–
Associated Q and S waves in different limb leads	5	–	4	2.6	–	–	–	–	1.3	2.6	–	–	–
RS-T segment deviations	29.5	2.6	15.6	6.5	4	8	2.6	13	–	6.5	–	1.3	8
T wave changes in Leads I and II	23	5.2	13	9	6.5	4	–	9	6.5	–	–	–	9
Inversion of the T wave in either Leads I or II	4	1.3	1.3	–	–	–	1.3	2.6	–	–	–	–	–

Heart Rate.—The observed heart rates varied from 60 to 150 per minute. Rates of 100 or more per minute were considered to justify a diagnosis of sinus tachycardia (Fig. 1). This condition was present in 36 patients (46.5 per cent). It was present as an isolated finding in only 4 per cent, while it was frequently associated with other changes such as prolonged duration of the P wave, RS-T segment deviations, and changes in the T waves (Table I). Sinus arrhythmia was present in seven patients but was not significant. Two examples of auricular and one of ventricular extrasystoles were recorded.

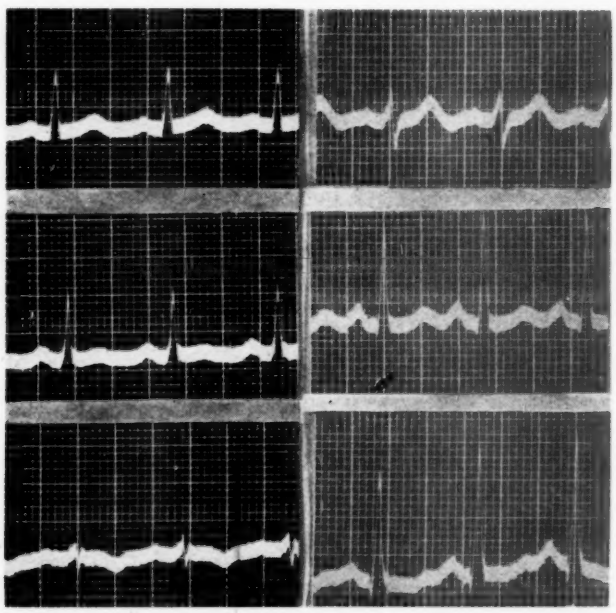


A. *B.* *C.*

Fig. 1.—Three records showing tachycardia. *A*, from a patient who complained of extreme weakness and palpitation, shows sinus tachycardia with a rate of 150 per minute. *B* is from a 28-year-old white man whose only complaint was weakness. The heart rate is 105 per minute with a P-R interval of 0.2 second. *C*, taken from a 22-year-old white man without symptoms, shows a heart rate of 111 per minute and premature auricular contractions.

P Waves.—Variations of the P waves (Fig. 2) were seen in 29 patients (38 per cent). These waves were abnormally wide in 23 patients (29.5 per cent); while notching appeared in only two. The electrocardiograms of four patients showed low P waves in the limb leads. The P-wave abnormalities were associated with sinus tachycardia; other associated changes were infrequent (Table I). In only one patient were abnormally high P waves seen.

P-R Interval.—Heart block was not present in any of the patients. However, in eight patients the P-R interval measured 0.2 second, and in nine an interval of 0.18 to 0.2 second was found. In all of these 17 patients an accompanying tachycardia was present. P-R intervals bordering upon the upper limits of normal were considered to have doubtful clinical significance, since slight prolongation is frequently seen in the convalescent period of various other infectious diseases.

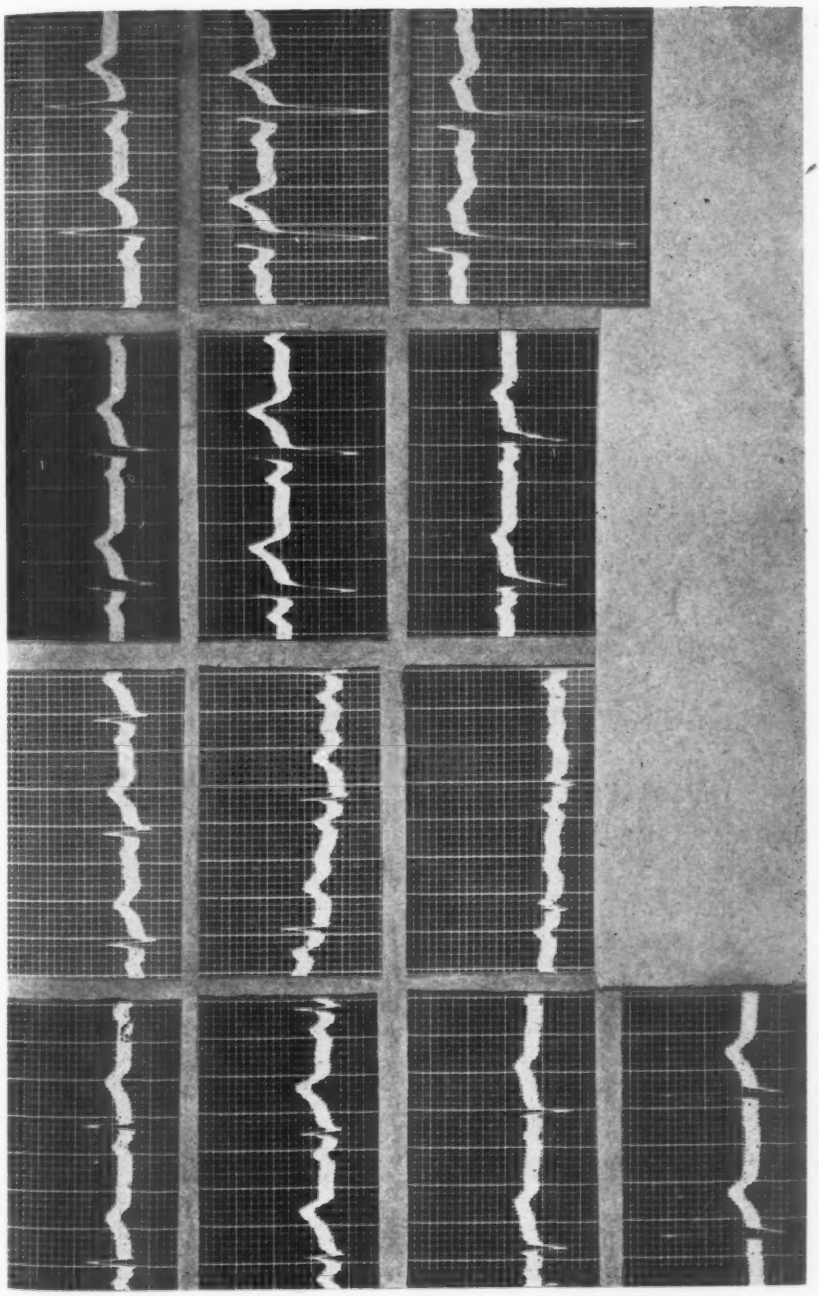


A. *B.*

Fig. 2.—Records indicating deviations of the P wave from the standards of normal. *A* is from a white man, 38 years old, with the complaint of weakness. *B* is from a 27-year-old white man who complained of palpitation and weakness and shows an increased duration of the P wave.

QRS Complex.—Abnormalities of the ventricular complexes were present in the majority of patients. These included the frequent presence of Q and S waves, low amplitude, and occasionally slurring and notching (Fig. 3). According to the criteria which is being applied, significantly large Q waves were seen in nine patients (12 per cent). In only four of these patients were there associated S waves in another lead. Small Q waves, not exceeding 25 per cent of the upward deflection, were present in 37 other patients. In this study, such small Q waves were considered to be a normal varient.

Deep S waves were present in 41 patients (53.2 per cent). Only those S waves which appeared in two or more of the limb leads were considered to be abnormal. This condition appeared in 21 patients (27 per cent). The QRS complex was of low voltage in ten patients (12.8 per cent). An abnormal duration of the QRS complex over 0.11 second was present in only one patient. Left axis deviation, which could not be attributed to the body build, was present in

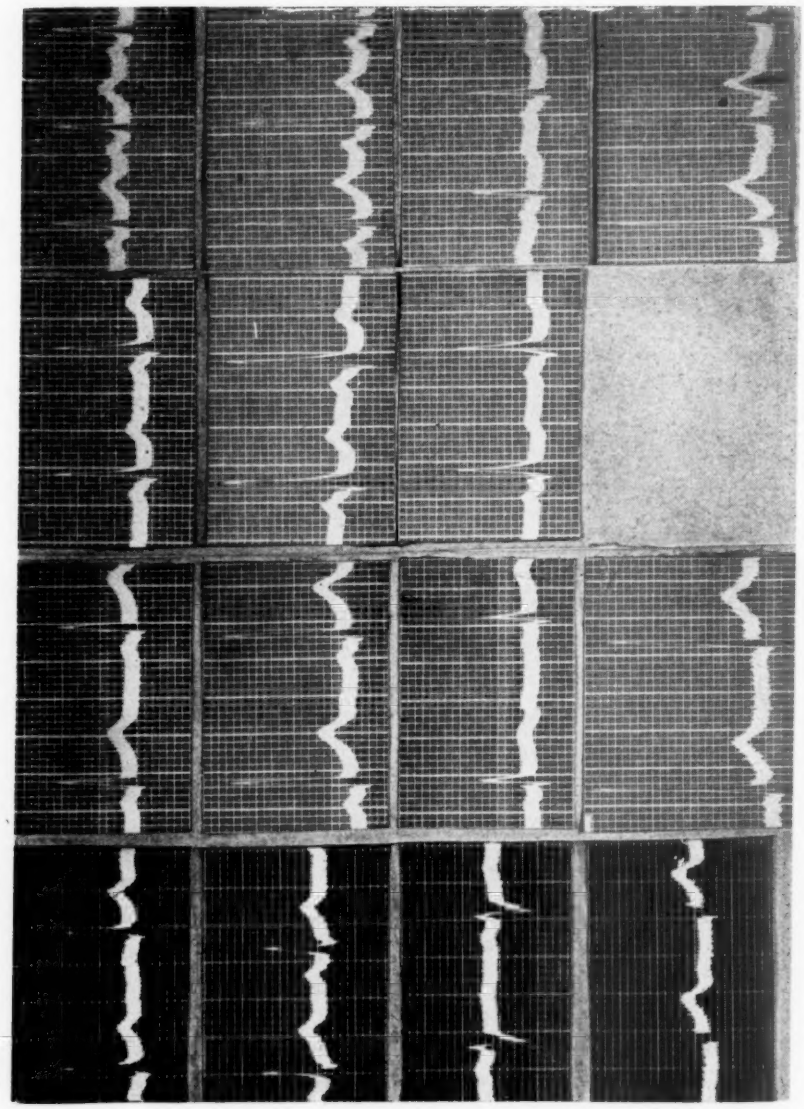


A. *B.* *C.* *D.*

Fig. 3.—Electrocardiograms from four cases showing examples of QRS-complex changes. *A* is from a patient, 35 years old, with no complants. It shows a heart rate of 90 per minute, with low voltage of the QRS complexes in the limb leads. *B* is from a patient, 30 years of age, who complained of weakness and fatigue. It shows a tachycardia with low voltage of the QRS complexes. *C*, from another patient, 31 years of age, who complained of precordial pain, dyspnea, and weakness, shows deep S waves and left axis deviation. *D* is from a 28-year-old patient who complained of weakness. The heart rate is 90 per minute and left axis deviation is present.

ten patients (12.8 per cent). Deviation of the axis to the right was found only once and in this instance was attributed to the body build of the patient.

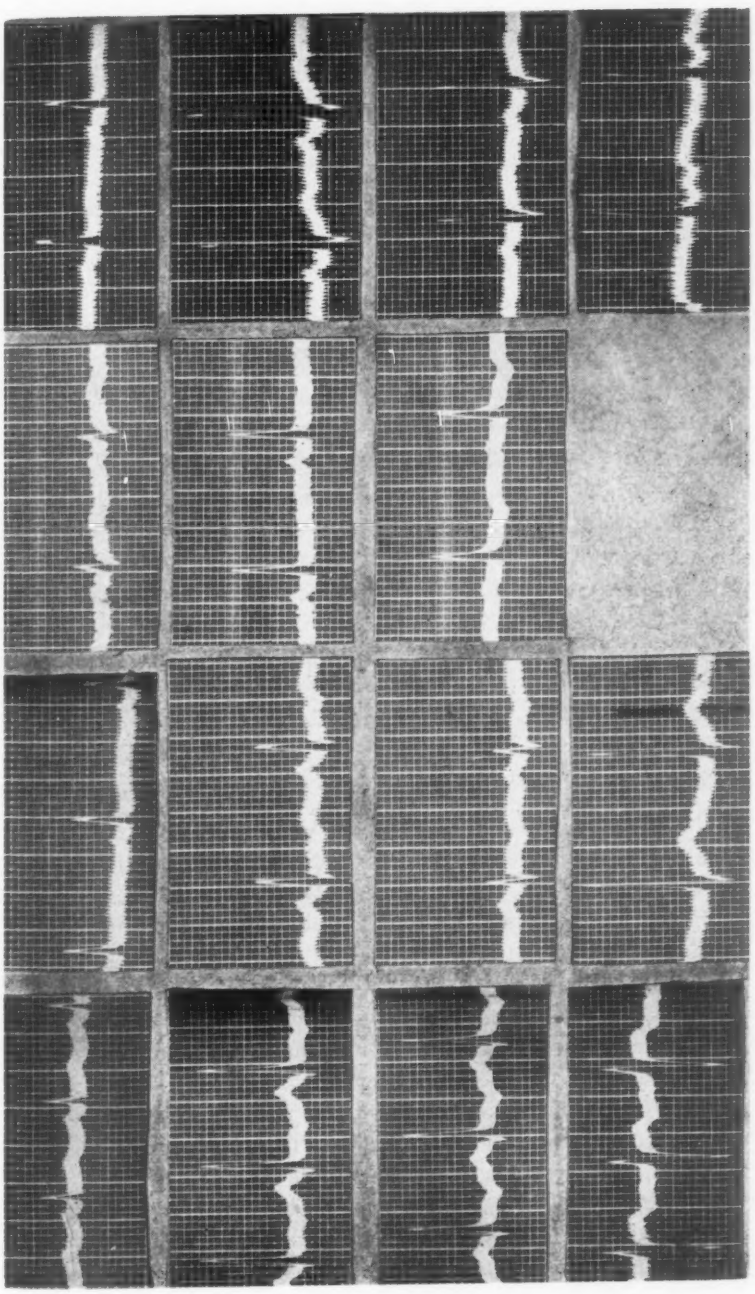
RS-T Segment.—Depression of the RS-T segment in the limb leads alone occurred in 12 patients (15.4 per cent). The depression was present in more



A. *B.* *C.* *D.*

Fig. 4.—Four instances of RS-T segment deviation. *A* is taken from a 25-year-old white man with complaints of substernal pain and weakness, and *B* is from another 25-year-old white man. Both show elevations of the RS-T segment. *D* and *E* show depression of the RS-T segments. *D* is taken from a 22-year-old white man, without complaints. *E*, from a patient aged 23 years, shows a tachycardia of which the patient complained.

than one limb lead in seven of the 12 patients. Depression of the segment was not noted in the precordial leads. Elevation of the segment was observed in 11 patients (14.1 per cent). This change was seen in the limb leads in 10 patients and in the precordial lead in one instance. The elevation was present in Leads II and III in three patients, in Leads I and CFIV in one patient, in Lead I alone in one patient, and in Lead II in five patients. The total number of RS-T



A. *B.* *C.* *D.*

Fig. 5.—Four examples of T-wave deviations. In *A*, from a 25-year-old white man, there is a heart rate of 120 per minute, with a low T wave in Lead I, diphasic T wave in Lead II, and an inverted T wave in Lead III. In *B*, which is from a 27-year-old white man, the heart rate is 90 per minute; low T waves are present in Leads I and II, and inverted T waves are present in Lead III. The RS-T segment in Lead II is depressed. *C*, from another white man, 24 years old, shows a heart rate of 90 per minute, low T waves in Lead I, an isoelectric T wave in Lead II, and inversion of the T wave in Lead III. Sinus arrhythmia is present. In *D*, from a 22-year-old white man, the rate is 90 per minute; the T waves are low in the limb leads and diphasic in the chest lead.

segment changes totaled 23 (30 per cent). Abnormal deviations were primarily associated with sinus tachycardia and abnormal S waves; in only 6.5 per cent were they associated with abnormal T waves (Table I). No example of both depression and elevation in the same record was recorded (Fig. 4).

T Wave.—In 23 patients (30 per cent) there were changes of the T waves which were confined to Lead III. In 16 of these 23 patients the change was inversion. These changes were considered to be within normal limits. In seven cases low T waves were observed in Lead I or II. Low waves were found in Lead I in three patients, in Leads I and III in two patients, and in all three leads in two patients. Associated with inversion of the T wave in Lead III were a low T wave in Lead I in four patients and low waves in Leads I and II as well as Lead III in four patients. In three cases inversion of the T waves in Leads II and III were associated with a low T wave in Lead I. Changes in the T waves, excluding changes limited to Lead III, were present in 18 patients (23 per cent). Of these only 5.2 per cent were isolated findings (Table I). Peaked T waves in the limb leads were present in two cases. T-wave abnormalities were not noted in the precordial leads (Fig. 5).

Duration of Changes.—The circumstances under which these studies were made allowed the study of only a limited number of these patients for any length of time. From those who could be followed for a number of months, no statistical conclusions could be drawn. In eight cases there was a persistence of the electrocardiographic abnormality as late as five months later, while in two the changes were present one year later. Frequently, the electrocardiogram would become entirely normal within three months of the onset of the infection. In other cases there would be some improvement with only the continuance of a minor abnormality.

SUMMARY

A study of the electrocardiographic findings in 78 patients convalescing from scrub typhus fever is reported. In 34.6 per cent of the patients of this series, symptoms referable to the heart were present. No relationship was found to exist between the subjective symptoms and the electrocardiographic findings. Likewise, no correlation between the severity of the disease and the apparent electrocardiographic abnormalities in the convalescent period could be determined. Patients who developed cardiac failure were more likely to show persistence of multiple abnormalities and to require a more prolonged convalescent period. The tracings of only 13 patients were graded as being within rigid normal limits; in another eight patients there were minor electrocardiographic changes that were placed within normal limits. The remaining 57 patients (73 per cent) showed abnormal electrocardiographic findings as late as six to eight weeks after the onset of the infection. Sinus tachycardia was present in 46.1 per cent and was frequently associated with some other abnormality. Prolonged duration of the P wave appeared in 29.5 per cent. No example of heart block was present. While minor deviations of the QRS complex were quite frequent, associated Q and S waves were present in the same record in only 5.2 per cent of the patients. Large S waves in more than two leads were found in

27 per cent. Low voltage was present in 12.8 per cent of the series. Small Q waves were present in 47.4 per cent of the series. Left axis deviation was seen in 12.8 per cent. In 29.5 per cent of the cases deviations of the RS-T segment occurred, and this was the only finding in 2.6 per cent of the patients studied. The T-wave abnormalities, excluding those in Lead III, totaled 23 per cent. Chest leads, with one exception, were within normal limits.

CONCLUSION

In this series of 78 cases of convalescent scrub typhus fever the electrocardiographic findings in the order of frequency were: (1) sinus tachycardia; (2) RS-T segment deviations, about equally divided between elevation and depression; (3) prolonged duration of the P wave; (4) abnormal S waves in at least two of the limb leads; (5) abnormalities of the T waves of which low amplitude was the most common; (6) left axis deviation; (7) diminished amplitude of the QRS complex; and (8) the presence of Q and S waves in different limb leads. Small Q and S waves were frequently noticed. Under a rigid application of the criteria defining the normal, apparent abnormal electrocardiographic findings were present in 73 per cent of the patients studied. In view of the somewhat wider limits of normal which are now accepted, some of these tracings would possibly be classified as within normal limits. However, the presence of borderline changes and particularly the presence of more than one change in a single tracing may well indicate the continued presence of myocardial damage.

No relationship between the severity of the disease, the subjective symptoms, and the presence and persistence of electrocardiographic abnormalities could be determined.

Acknowledgment is made to Lieutenant Colonel Carl A. Dahlgren and Major Herman Shapiro for their cooperation and helpful suggestions.

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Clinical Reports

PERSISTENT RIGHT AORTIC ARCH WITH ATRESIA OF THE ENTIRE MAIN PULMONARY ARTERY

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VERY early in the development of the human embryo the definitive aortic arch and its branches and the pulmonary artery have their origin in a series of arches that develop between the ventral and dorsal aortae.[1] These are six in number and arise in consecutive order cephalocaudally. By means of atrophy and absorption, certain portions of the arches disappear completely whereas others remain to form the adult vessels as we know them. While the pattern of atrophy and absorption is ordinarily remarkably constant, occasionally it is not, and this results in the formation of a series of anomalies of the larger vessels which also pursue definite patterns.

The most common abnormalities are found in the aortic arch and its branches and consist of coarctation of the aorta, patent ductus arteriosus, posterior right subclavian artery, right-sided aortic arch, and double aortic arch.[2] Anomalous developments of the main pulmonary artery also occur, but these are considerably less common.

Perhaps the most frequently encountered anomaly of the pulmonary artery is stenosis of the origin of the main artery so constantly found as one of the features of the tetralogy of Fallot. Complete stenosis or atresia at the exit of the main pulmonary artery from the right ventricle has been reported quite frequently.[3-5] Complete or partial absence of the main pulmonary artery has been recorded less often. In 1928, Wheeler and Abbott[6] reported a case of the latter in a man 29 years of age. In 1931, Kugel[7] described two cases in infants, and, in reviewing the literature, stated that Abbott collected 31 cases of "truncus solitarius aorticus." Subsequently, a case in a girl 9 years old was reported by Schopper,[8] one in a boy 5 years old was reported by Greenspan and Leaman,[9] and one in an infant 9½ months old was reported by Rossman.[10] In the last 1,200 necropsies performed at the Jefferson Medical College Hospital we have encountered eight cases of a posterior right subclavian artery, three cases of a patent ductus arteriosus, two cases of a double aortic arch, one case of a right-sided aortic arch, and one case of a right-sided aortic arch with an atresia of the

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entire main pulmonary artery. The latter is of particular interest because in a review of the literature we have found only one other case in which this combination was present.[6]

REPORT OF A CASE

A white girl was delivered spontaneously at term and for the first two days of extrauterine life appeared entirely normal. On the third day she developed repeated attacks of cyanosis and was admitted to the Jefferson Medical College Hospital. When the first bottle feeding was attempted at the hospital she suddenly developed deep cyanosis unaccompanied by signs of respiratory or esophageal obstruction. The feeding was immediately stopped and, aided by inhalations of oxygen, her normal color returned. Subsequently cyanosis recurred at each attempt at feeding or on crying. By the end of the day, however, cyanosis became continuous and disappeared only when the child was placed in an oxygen tent. Feedings could now be administered only with a medicine dropper.

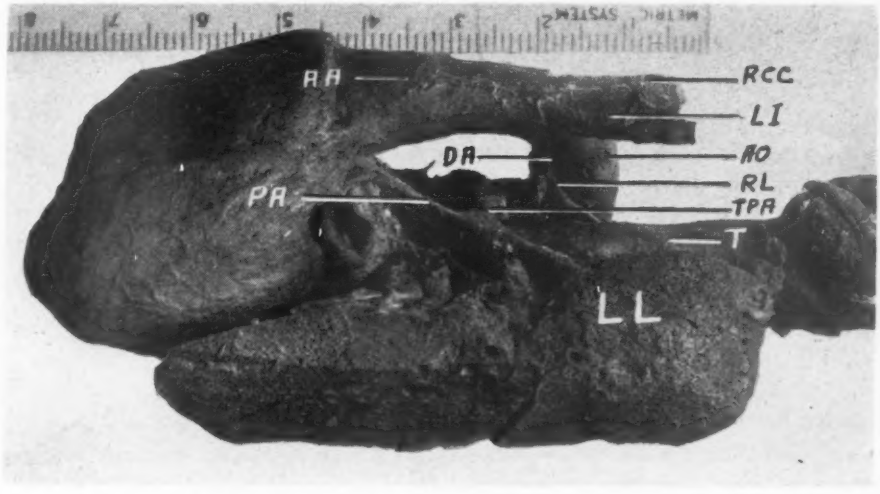

Fig. 1.—Left lateral view showing: *AA*, ascending aorta; *RCC*, right common carotid; *LI*, left innominate; *AO*, right aortic arch; *DA*, ductus arteriosus; *RL*, right recurrent laryngeal nerve; *TPA*, transverse pulmonary arch; *PA*, atretic main pulmonary artery; *T*, trachea; and *LL*, left lung.

Physical examination revealed the cyanosis of the head and neck already referred to. There were a slight shift of the trachea to the right at the suprasternal notch, a lag in the expansion of the chest on the right, impaired percussion, and diminished breath sounds over the right upper lobe. There were no abnormalities on percussion or auscultation of the heart at the initial or subsequent examinations. A roentgenogram of the chest on the day of admission revealed an atelectasis of the upper lobe of the right lung, a slight displacement of the esophagus and mediastinum to the right, and a normal-appearing heart shadow. A bronchoscopic examination by Dr. Louis H. Clerf disclosed a normal larynx, trachea, and main bronchi, with no apparent obstruction of the bronchus to the right upper lobe. A culture of the bronchial secretions yielded *Streptococcus viridans*, a member of the Friedlander group of organisms, and *Neisseria catarrhalis*. An electrocardiogram disclosed a right axis deviation compatible with a congenital heart lesion. Some clubbing of the finger tips was noted on the sixth day after admission. A second bronchoscopic examination on the ninth day did not reveal any changes. Cyanosis continued and the child died on the fourteenth day of extrauterine life.

At necropsy the entire main pulmonary artery originating at the base of the aorta and ending in a "transverse pulmonary arch" was represented by a solid fibrous cord that

measured 1.5 by 0.1 cm. (Figs. 1 and 2). The left pulmonary artery was widely patent and measured 0.4 cm. in diameter and 1 cm. in length from the entrance of the fibrous cord to the hilum of the left lung. The right pulmonary artery was directly continuous with the left, and from the entrance of the atresic main pulmonary artery to the hilum of the right lung measured 1 cm. in length and 0.5 cm. in diameter. At a point 0.4 cm. from the hilum of the right lung it received a patent right ductus arteriosus that measured 1.5 cm. in length and 0.4 cm. in diameter. This entered a persistent right aortic arch just distal to the junction of the arch with the ascending aorta. The ascending aorta measured 2.3 cm. in length and 1.2 cm. in diameter and at the arch gave rise to the following main arteries: left innominate, right common carotid, and right subclavian. The aortic arch was directed posteriorly to the right of the trachea and esophagus and ended in the descending aorta which gradually crossed to the left side behind the esophagus. The bronchial arteries were not hypertrophied. The right

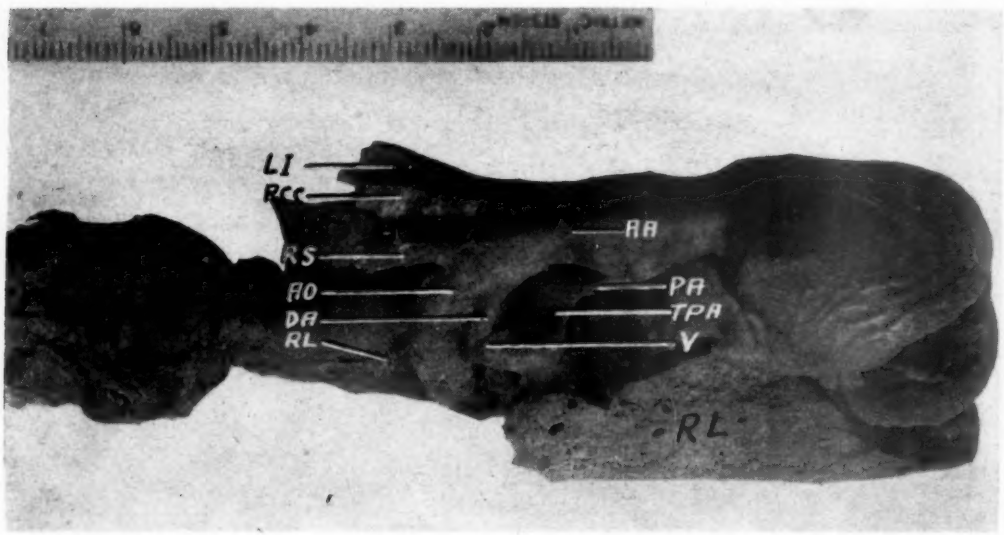

Fig. 2.—Right lateral view showing: *AA*, ascending aorta; *LI*, left innominate; *RCC*, right common carotid; *RS*, right subclavian; *AO*, right aortic arch; *DA*, ductus arteriosus; *RL*, right recurrent laryngeal nerve; *PA*, atretic main pulmonary artery; *TPA*, transverse pulmonary arch; *V*, vagus nerve; and *RL*, right lung.

vagus nerve was normal in position and gave off the right recurrent laryngeal nerve as it crossed the ductus arteriosus. It wound around the latter and ascended to the larynx in the tracheoesophageal groove. The right atrium of the heart was considerably dilated; the foramen ovale was widely patent; the superior four-fifths of the interventricular septum was defective; and the ascending aorta straddled this defect. The lungs showed scattered patchy atelectasis throughout all the lobes and irregular areas of pneumonia. The only other congenital anomalies present were a mobile cecum and a partial failure of rotation of the entire intestines.

COMMENT

The definitive arterial pattern as seen in this case is readily explained on an embryological basis.[11] The aortic arch and its branches normally develop from the fourth pair of aortic arches first seen in the 5 to 6 mm. stage embryo. Ordinarily, the fourth arch on the left side persists in its entirety forming the normal aortic arch, while on the right side the dorsal portion between the entrance of the seventh cervical segmental artery (or what later becomes the distal part of the right subclavian artery) and the descending aorta disappears. The en-

tire ventral portion of the fourth arch thus becomes the proximal portion of the right subclavian artery. The common carotid arteries come from the proximal portions of the third arches. On the left side, this, together with the proximal portion of the aortic sac, is incorporated directly into the aortic arch, whereas on the right side the portion of the aortic sac where the ventral part of the fourth arch joins the right common carotid artery then elongates and forms the innominate artery.

One has, normally, therefore, a left aortic arch giving off in order the right innominate artery, the left common carotid artery and the left subclavian artery (which comes entirely from the seventh left cervical segmental artery). The case reported here is a mirror image of the normal, as just described, so that there is a righ-sided aortic arch giving off, in order, a left innominate artery, a right common carotid artery, and a right subclavian artery.

The pulmonary arteries arise from the sixth aortic arches, which first appear in the 6 mm. stage of the developing embryo. As a result of growth and absorption, the proximal portions persist as the main pulmonary artery and the right and left branches, whereas the distal portion on the right side disappears and that on the left forms the ductus arteriosus. In our case the main pulmonary artery became atresic and was represented by a fibrous cord, but there was a direct communication between the right and left pulmonary arteries, forming a normally functioning transverse pulmonary arch. The portion of the left sixth arch that usually forms the ductus arteriosus had disappeared while that on the right side was represented by a widely patent vessel. It was by means of this right ductus arteriosus that the pulmonic circulation was maintained receiving both aerated and nonaerated blood from the ascending aorta.

The literature on a right-sided aortic arch has been adequately covered several times, and a summary need not be repeated here.[12, 13] This anomaly of itself usually produces no symptoms until later life.[14, 15] when, as a result of sclerotic changes, the aorta may dilate and press upon the esophagus, trachea, or right recurrent laryngeal nerve. In the case reported by Herringham[16] a dilated aorta produced right-sided laryngeal paralysis and death from tracheal compression. Jex-Blake[17] reported a case of a right aortic arch in a puppy where a short ductus arteriosus coursing first to the left and then behind the esophagus produced esophageal obstruction. Other signs and symptoms that may be elicited are: suprasternal pulsation, stridor, hoarseness, cough, pain in the chest, sensation of "pins and needles" in the left arm, difficulty in eliciting the left radial pulse, and a pulsating tumor identing the wall of the trachea and esophagus as visualized by tracheoscopy and esophagoscopy.[13, 14, 18] Since most of the cases are asymptomatic, an ante-mortem diagnosis of a right-sided aortic arch rests with the roentgenologist.[19, 20] Of importance is a widening of the upper mediastinal shadow to the right instead of to the left and, fluoroscopically, a pulsating aorta to the right of the trachea. When the left aortic arch persists as a diverticulum there may be an aortic knob on both sides of the upper mediastinum. Examination of a barium-filled esophagus shows a characteristic concave depression on the right side at the level of the pulsating shadow, while in the right anterior oblique view the depression is seen on the posterior wall of

the esophagus, and both the esophagus and trachea are displaced anteriorly. Finally, arterial radiography[21] allows direct visualization of the aortic arch to the right of the trachea and above the hilum of the right lung. Because our case exhibited cyanosis alone it is unlikely that the right aortic arch contributed to its symptoms. A single film of the chest showed no abnormal arterial shadows. Barium studies of the esophagus and arteriography were not attempted because the child was too ill, but bronchoscopic examinations disclosed no tracheal compression.

Although a right-sided aortic arch produces few if any symptoms, stenosis or atresia of the main pulmonary artery is rarely asymptomatic. Cyanosis and dyspnea are usually present from birth,[5, 7, 10] and if the patients live beyond infancy there may develop clubbing of the fingers, a precordial thrill, systolic and diastolic murmurs over the precordium, polycythemia, and venous distention of the neck. Death results from cardiac failure or intercurrent infection.[5, 7, 9]

The prognosis is not good and depends on the extent of the collateral circulation which, however, cannot be ascertained clinically. The arteries that may establish a collateral circulation[22] consist of the ductus arteriosus, the bronchials, and the mediastinal, esophageal, precordial, coronary, and aberrant arteries from the aorta or subclavian artery. From a study of the cases that came to necropsy it would appear that the best prognosis occurs in those with hypertrophy of the bronchial arteries. In the nine cases reviewed in this report, those showing a closed ductus arteriosus and hypertrophied bronchials[5, 9, 22] lived to the ages of 5, 16, 20, and 33 years; those showing a partially patent ductus arteriosus and hypertrophied bronchials[6, 8] lived to the ages of 9 and 29 years, while those with a patent ductus and small bronchials[7, 10] died at 6 months, 9½ months, and 14 months of age. In our case the bronchials were not hypertrophied; the ductus arteriosus was patent, and the child died at the age of 14 days.

Treatment in stenosis or atresia of the main pulmonary artery has hitherto been entirely symptomatic and at best rather disappointing. The work of Blalock and Taussig,[23] however, has changed the entire outlook. In three children showing severe cyanosis resulting from stenosis or atresia of the main pulmonary artery they increased the flow of blood to the lungs by anastomosing the subclavian or innominate artery to a pulmonary artery. Clinically there was immediate improvement in that there occurred a decrease in cyanosis, decrease in dyspnea, and an increase in tolerance to exercise. If this improvement can be maintained there is new hope for an otherwise almost universally fatal condition. This alone justifies the reporting of as many cases as possible in order to enable a more accurate clinical diagnosis.

SUMMARY

Of the many anomalies that may arise from the primitive aortic arches present in the developing human embryo, atresia of the main pulmonary artery is one of the least frequently encountered. A combination of this abnormality with a right-sided aortic arch is even less frequent, for the literature contains only one report of such a case. The case presented here is that of an infant who

developed cyanosis two days after birth and died on the fourteenth day of extrauterine life. At necropsy there were found atresia of the entire main pulmonary artery, a right-sided aortic arch, a patent right ductus arteriosus, interauricular and interventricular septal defects, and dextroposition of the aorta.

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PRIMARY, MASSIVE CALCIFICATION WITH OSSIFICATION OF THE MYOCARDIUM

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PRIMARY, massive calcification of the myocardium with bone formation is very rare. Its occurrence in the myocardium of the left ventricle of an 11-year-old boy was observed at autopsy.

Scholz,[1] in 1924, reviewed the literature on the subject of calcification of the heart and compiled a list of thirty cases. Diamond[2] reported a 26-week-old premature infant with extensive calcium deposits in degenerated heart muscles. This he attributed to unknown toxic causes. Brown and Evans,[3] in 1939, were able to find records of only fourteen instances of primary, massive calcification of the myocardium. Coronary artery disease existed in all but four of these fourteen cases. These authors reported as primary, an instance of massive calcification of the heart muscle which was evidently secondary to coronary artery disease. They stated that massive myocardial calcification usually follows occlusive coronary disease.

CASE REPORT

An 11-year-old white boy was admitted to the hospital because of bradycardia, easy fatigability, and slight cough. The past history disclosed scarlet fever at the age of 6, and rheumatic fever at the age of 7 years. For the past year slight exertion had produced extreme fatigue and epigastric pain. For the past seven months he had been confined to his bed. The physical examination disclosed a poorly nourished child. There were increased breath sounds and moist râles over the lungs. Examination of the heart revealed a loud first sound at the apex, a duplication of the second sound, a questionable third sound, and a gallop rhythm. The second pulmonic sound was accentuated. The left border of the heart was at the anterior axillary line, and the apex was felt in the sixth intercostal space. The heart rate was 60 per minute and the arterial blood pressure was 124/85. The liver was considerably enlarged.

During his stay in the hospital the heart rate was 48 per minute on several occasions, and a "swishing" systolic murmur was heard at the left of the sternum in the third and

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Fig. 1.—Heart (left ventricle). Note the marked deposition of calcific material throughout the myocardium.

Fig. 2.—Mitral orifice. Note the narrowing of this orifice brought about by calcific material in the myocardium in the region of the mitral ring.

Figs. 3 and 4.—X-ray pictures of the heart. Note the dense shadows.

Fig. 5.—Microphotograph of the myocardium. Iron-hematoxylin-eosin preparation; magnification, ×130. Note the hyalinization, calcification, and the remnants of muscle fibers.

Fig. 6.—Section of the myocardium. Iron-hematoxylin-eosin preparation; magnification, ×90. Note the absence of heart muscle fibers in the vicinity of the calcified material, and the moderate infiltration of lymphocytes.

FIG 1.

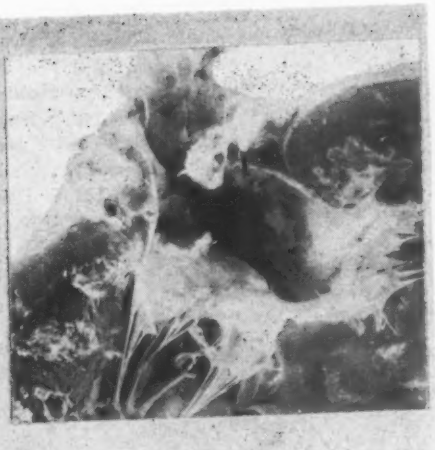

FIG 2.

FIG 3.

FIG 4.

FIG 5.

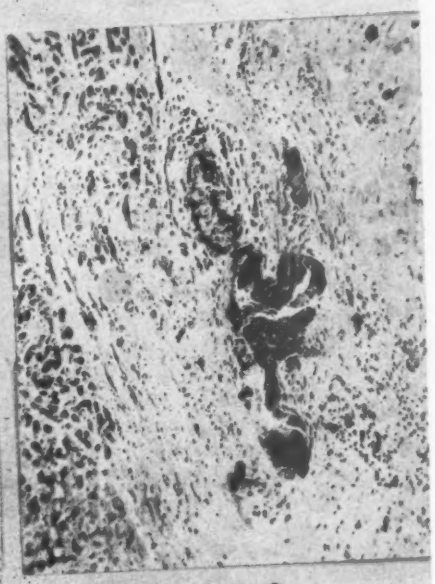

FIG 6.

Figs. 1-6.—(*For legends see opposite page.*)

fourth intercostal spaces. After the patient was digitalized, a rough presystolic murmur became audible at the apex. The pulse was regular but small in volume. The clinical diagnosis was rheumatic heart disease with mitral stenosis.

The electrocardiographic interpretation was, "Sinus rhythm, with complete A-V block. The idioventricular rhythm arises below the bifurcation of the common A-V bundle." (Fig. 7.) The x-ray examination showed the heart to be markedly enlarged both to the left and right. The lung fields showed a marked degree of pulmonary congestion and there was a small amount of pleural fluid in the right base. The x-ray diagnosis was, "Cardiac enlargement, probably combined mitral pathology."

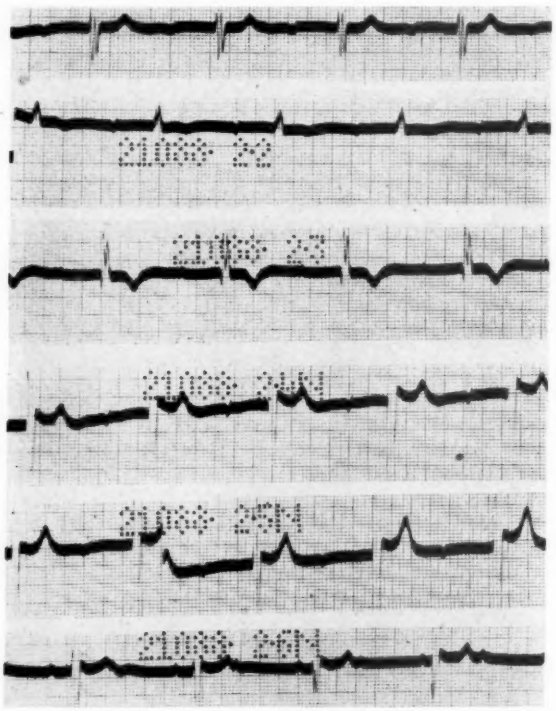

Fig. 7.—Electrocardiogram showing Leads I, II, and III and chest leads CF_2, CF_4, and CF_5. The auricular rate, clearly seen in CF_5, is 94; the ventricular rate is 48. The two rhythms are regular; the varying P-R distance indicates complete A-V block. The QRS complex is prolonged, measuring 0.12 second; this indicates origin of the idioventricular pacemaker below the bifurcation of the common bundle.

Repeated blood cultures were sterile. The urinary findings were not abnormal. The red blood count was 5,950,000; the hemoglobin determination, 93 per cent; the leucocyte count, 12,000. There were 57 polymorphonuclear leucocytes, 38 lymphocytes, and 5 monocytes. The Wassermann and Kahn reactions were negative.

The patient died rather unexpectedly five weeks after admission to the hospital.

At autopsy marked edema was found in both lower extremities. The peritoneal cavity contained 1,000 c.c. of clear straw-colored fluid. Each pleural cavity contained about 700 c.c. of the same sort of fluid. Within the pericardial sac, 150 c.c. of a similar fluid were found. The serous surfaces throughout were smooth and glistening, and there were no adhesions.

The heart was markedly enlarged, weighing 500 grams. It was very firm and masses which were of stony hard consistency were palpable throughout both right and left ventricles (Figs. 1, 3, and 4). Only very small portions of the heart wall were of normal consistency. It was extremely difficult to dissect the heart in the usual way because the

calcific masses could not be cut with the knife or scissors, and it had to be opened by means of a hand saw. The valvular apparatus was intact. However, the orifice of the mitral valve was distinctly narrowed by calcific masses which were present in the adjacent myocardium and had severely compressed the mitral orifice which barely permitted the introduction of one finger (Fig. 2). The tricuspid valve measured 8 cm. in circumference, the pulmonic, 6 cm., the mitral, 3 cm., and the aortic, 5 cm., respectively. When the myocardium was examined, it was noted that the left ventricle was almost completely rigid with only isolated portions of relatively normal myocardium. It was difficult to understand how such severely calcified muscle could maintain the function of the heart. The mouths of both coronary arteries were patent. The coronary arteries themselves showed no change. The right ventricle measured 0.5 cm. in thickness; the left measured 1.4 centimeters.

The examination of the remaining organs disclosed a very severe chronic passive hyperemia and terminal bronchopneumonia.

Histologic examination of sections of the myocardium stained with hematoxylin and eosin showed many areas of lymphocytic infiltration in the interstitial tissue, much fibrosis, and large areas consisting of amorphous, bluish material (Figs. 5 and 6). This stained black by the von Kossa method. In many fields, in addition to the bluish amorphous material, unmistakable ossification was noted.

In summary, an 11-year-old child, with severe respiratory difficulties, died as a result of severe calcification of the myocardium.

COMMENT

It is usually stated (Karsner[4]) that pathologic calcification may be divided into dystrophic and metastatic forms. In dystrophic calcification, calcium is deposited in tissues and cells which are the seat of disease. Thus, foci of dense fibrosis, especially if hyalinized, and necrotic masses may become infiltrated with calcium. Dystrophic calcification often attains sufficient size to be seen grossly, as for example, in the wall of the aorta. Metastatic calcification differs from the dystrophic form in that there is no clearly identified tissue injury as a precursor and in that calcium is mobilized from its natural depots. The calcification occurs in the veins, capillaries and alveolar septa of the lungs, in the endocardium of the left side of the heart, in the tunica propria of the acid-secreting parts of the mucosa of the stomach, and in tubules and connective tissue of the kidneys, as well as in other situations. MacCallum[5] stated that it is questionable whether calcium is ever deposited in the bodies of living active cells, and that one gains the impression that its deposit always occurs in hyaline, inert, interstitial substance, or in dead cells.

Because of the fact that the myocardium was the only region in the body where calcification was present, it seems unlikely that this is an instance of metastatic calcification. It is more likely that the severe myocardial calcification is dystrophic in nature. It seems likely that the calcification was preceded by degenerative and necrotizing lesions in the myocardium.

Among the diseases causing such lesions, diphtheria occupies a prominent place. Ceelen[6] stated that the toxin of the *Corynebacterium diphtheriae* may produce parenchymatous degeneration and at times even calcification of the myocardium. In one instance of diphtheria he observed partial calcification of the fibers of the right bundle branch and also calcification within the myocardium. Kratzeisen[7] observed at autopsy the heart of a patient who died as

a result of diphtheria. A deposition of calcium was seen within the diseased muscle fibers.

Also interesting in this respect are the experiments of Albrecht[8] who seemingly succeeded in producing calcification of heart muscle fibers in rabbits by the injection of *Haemophilus influenzae*. A case of massive calcification of the myocardium of the type reported by Brown and Evans[3] is apparently of a different nature since degenerative changes in the heart of this patient were the result of coronary arteriosclerosis with massive calcification.

Although it was impossible to elicit a definite etiological agent for degenerative lesions in the myocardium, which presumably had preceded the calcification of the myocardium, it seems most likely that the patient had either diphtheria or an infection brought about by *Haemophilus influenzae,* since these are the two diseases which more commonly produce degeneration and even necrotizing lesions in the myocardium.

SUMMARY

An instance of massive calcification with bone formation in the myocardium of an 11-year-old boy is reported. No definite etiology for this disease is manifest, but it seems that either diphtheria or infection with *Haemophilus influenzae* had produced degenerative changes and necrotizing lesions of the heart muscle with secondary calcification. The heart was the only organ in the body which showed calcification.

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MULTIPLE DISTURBANCES OF RHYTHM AND CONDUCTION AND UNUSUAL AURICULAR T WAVE IN A CASE OF MYOCARDIAL INFARCTION

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NEWARK, N. J.

RECENT experimental and clinical reports have stimulated interest in the possibility of making the diagnosis of auricular infarction by means of the electrocardiogram.[1-3] The presence of auricular infarction is suggested by disturbances of the auricular mechanism, and by abnormalities in the contour of the auricular complex. The following auricular arrhythmias are encountered: auricular fibrillation, flutter, premature contractions and paroxysmal tachycardia, sinus arrest, wandering pacemaker, and A-V nodal rhythm. Changes involving both the initial and final auricular deflections occur, which are analogous to the evolution of the QRS-T changes which result from infarction of the ventricles. Thus, an auricular Q or S wave may appear, the P wave may be inverted, broadened, increased or diminished in amplitude, notched or slurred, or M- or W-shaped complexes may develop. The auricular S-T segment (P-Q or P-T_A segment) may deviate abnormally, and abnormal auricular T waves may be seen.

The potential differences set up by the final phase of auricular activity are most often so minute as to fail to register in the electrocardiogram. Furthermore, since the total duration of auricular electrical systole exceeds the normal P-R interval, the late deflections are buried in the following QRS complex. In experimental studies the A-V conduction system is blocked mechanically before auricular infarction is produced so that the entire cycle of electrical activity in the auricles is recorded. Since in man the coincidence of auricular infarction with prolonged A-V conduction is rare, little clinical data concerning abnormalities of the final auricular deflection have been accumulated.

It was thought worth while, therefore, to report the following case in which, after an attack of coronary occlusion, multiple disturbances of rhythm and conduction and an unusual auricular T-wave pattern developed.

CASE REPORT

J. G., a 52-year-old Italian man, was admitted to the Cardiac Clinic on May 5, 1943, complaining of shortness of breath and edema of the legs. He was a bartender by occupation and had been a heavy drinker most of his life. He admitted to having had two attacks of gonorrhea but denied syphilitic infection. His wife was a known syphilitic, but repeated examinations in the past had not established the presence of syphilis in the patient. He had considered himself well until July, 1940, when he experienced an attack of substernal pain radiating to the left shoulder. This was followed shortly by severe dyspnea and cough, and

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later by edema of the legs. During the next three years he was admitted to various hospitals on five occasions for the treatment of congestive heart failure. Between bouts of failure he had been able to continue work. Electrocardiograms which were taken during this time on ten occasions showed auricular flutter with varying degrees of incomplete A-V block and right bundle branch block.

The essential physical findings on admission to the clinic were as follows: Dyspnea, orthopnea, and cyanosis were evident. The neck veins were distended. The pulse appeared regular, with a rate of 60 per minute. Blood pressure was 135/80. The heart was enlarged to the left. No thrills or abnormal pulsations were elicited. The rhythm was apparently regular. The first sound was split at the apex, and a faint systolic murmur was audible in this area. The liver edge was palpable 3 fingerbreadths below the right costal margin. The spleen was not palpable. There was no demonstrable ascites. The lower extremities were markedly edematous.

An x-ray film of the chest revealed an old fibrous infiltration of the left upper lobe. The heart was enlarged, chiefly to the left, and there was passive congestion of the lung fields. Electrocardiogram on admission showed auricular flutter with four-to-one A-V block, right bundle branch block, premature ventricular contractions, and ventricular escape beats. The urine showed occasional albumin and showers of hyaline and granular casts. The blood count and blood chemistry were within normal limits. The blood Wassermann reaction was negative.

The diagnosis on admission was (a) arteriosclerotic heart disease; (b) hypertrophy and dilation, coronary sclerosis, myocardial infarction; (c) auricular flutter, right bundle branch block, premature ventricular beats, ventricular escape beats, cardiac insufficiency; and (d) Class IV.

Clinical Course.—The patient was digitalized and placed on a regime of limited fluid intake, salt-free diet, ammonium chloride, and Mercupurin. On July 15, 1943, complete A-V block with auricular flutter and short paroxysms of ventricular tachycardia were noted. This was considered an indication to withdraw digitalis. Five weeks later, auricular fibrillation appeared and digitalis therapy was resumed. On Nov. 4, 1943, while the patient was still on a full maintenance dosage of digitalis, normal sinus rhythm was restored. Coincidentally, there was marked clinical improvement, and aside from dyspnea on exertion, all manifestation of congestive failure disappeared. On Feb. 12, 1944, while walking on the street, he suddenly collapsed; he died shortly after admission to the hospital. Unfortunately, a post-mortem examination was not performed.

ANALYSIS OF ELECTROCARDIOGRAMS

Electrocardiograms were obtained on twelve occasions. Routine findings will be summarized in this section while unusual features will be discussed in detail.

May 20, 1943 (Fig. 1, *A*): Auricular flutter with four-to-one A-V block was present. The auricular rate was approximately 230 per minute, and the ventricular rate was 58 per minute. The flutter waves were of low voltage. The QRS interval measured 0.14 second and there was right bundle branch block. Occasional premature ventricular beats and ventricular escape beats were seen.

June 3, 1943 (Fig. 1, *B*): Findings were essentially the same. A precordial lead, which was taken with the exploring electrode placed over the third right intercostal space, demonstrated flutter waves conclusively.

July 15, 1943: Auricular flutter was still present with varying A-V block and intermittent complete A-V block. Lead I was of particular interest (Fig. 2). Auricular flutter was present at a rate of about 222 per minute. The first ventricular complex was indicative of right bundle branch block. The next

five ventricular beats were of the left bundle branch block type. They occurred in a perfectly regular rhythm, with an R-R interval of 1.52 seconds, and with dissociation from the auricular rhythm, indicating complete A-V block. The bundle branch block then shifted again to the right side, and there was a sequence of three ventricular beats of this type. The change from right to left bundle branch block occurred after a long pause of 1.66 seconds duration, while the shift from left to right bundle branch block occurred after an interval which

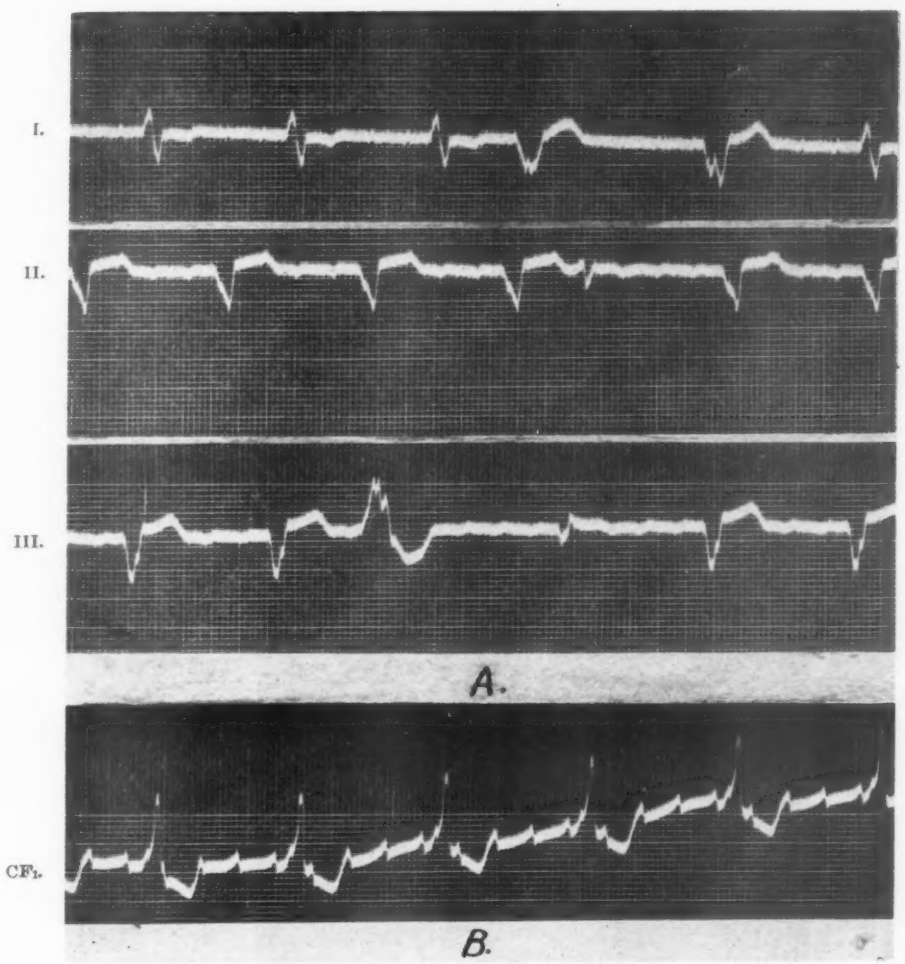

Fig. 1.—*A*, May 20, 1943. Auricular flutter, four-to-one A-V block, right bundle branch block, premature ventricular contractions, and idioventricular escape beats. *B*, June 3, 1943. Precordial lead, with exploring electrode over third right intercostal space. Flutter waves are shown more distinctly.

was shorter than that between idioventricular beats, that is, 1.32 seconds. The QRS complexes of the right bundle branch block type were assumed to have been in response to an auricular impulse. This type of complex was seen invariably when either auricular flutter, auricular fibrillation or normal sinus rhythm was present without complete A-V block (Figs. 1, 3, 4, and 6). On

the other hand, complexes of the left bundle branch block type were encountered when complete A-V block was present, either with auricular flutter or normal sinus rhythm (Figs. 2 and 5). This suggests that the idioventricular pacemaker under the latter circumstances was situated in the right bundle branch below the area of block in this bundle. An alternate explanation would be that during

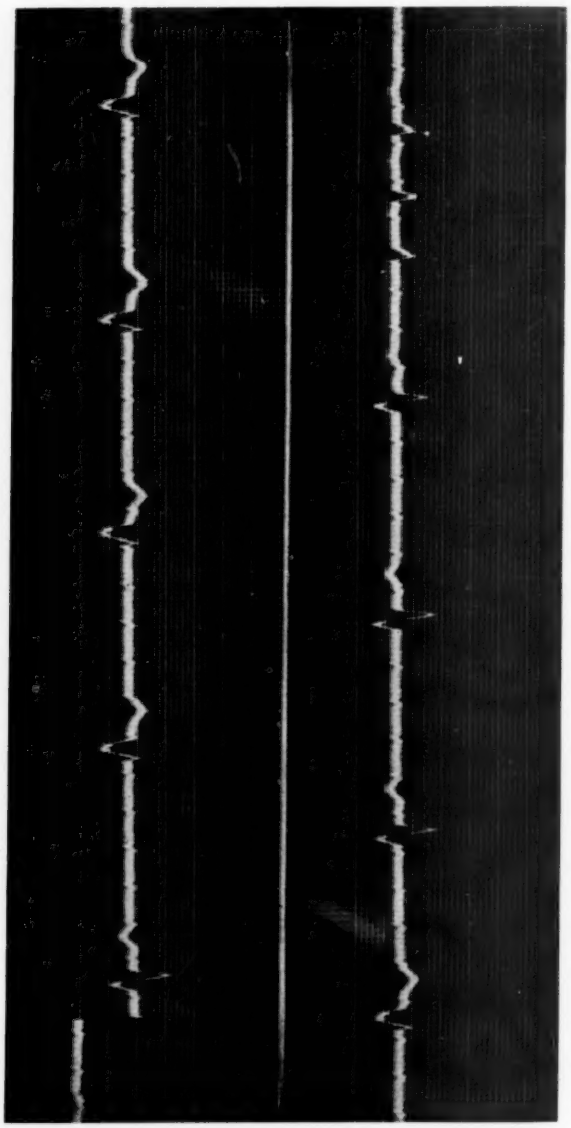

Fig. 2.—July 15, 1943. Lead I, continuous tracing. Auricular flutter. First, seventh, eighth, and ninth ventricular complexes are of right bundle branch block type. Second to sixth ventricular complexes, inclusive, left bundle branch block, and complete A-V block. Last three ventricular complexes constitute a brief paroxysm of tachycardia.

complete A-V block the idioventricular pacemaker might be located above the bifurcation of the bundles. The impulse might then take a slightly different pathway which would allow it to pass through the area of block in the right bundle branch. In support of this hypothesis, when an apparent A-V nodal

rhythm was present (Fig. 6), the ventricular complexes were of the left bundle branch block type. The last three beats of Fig. 2 were ventricular premature beats, constituting in effect a short paroxysm of ventricular tachycardia. The QRS interval of these beats was shorter than the normal, and, therefore, they probably originated in the region of the interventricular septum.

July, 22, 1943: Auricular flutter, four-to-one block, A-V and right bundle branch block were present.

July 29, 1943: There was no change.

Aug. 26, 1943: Auricular fibrillation and right bundle branch block were present (Fig. 3).

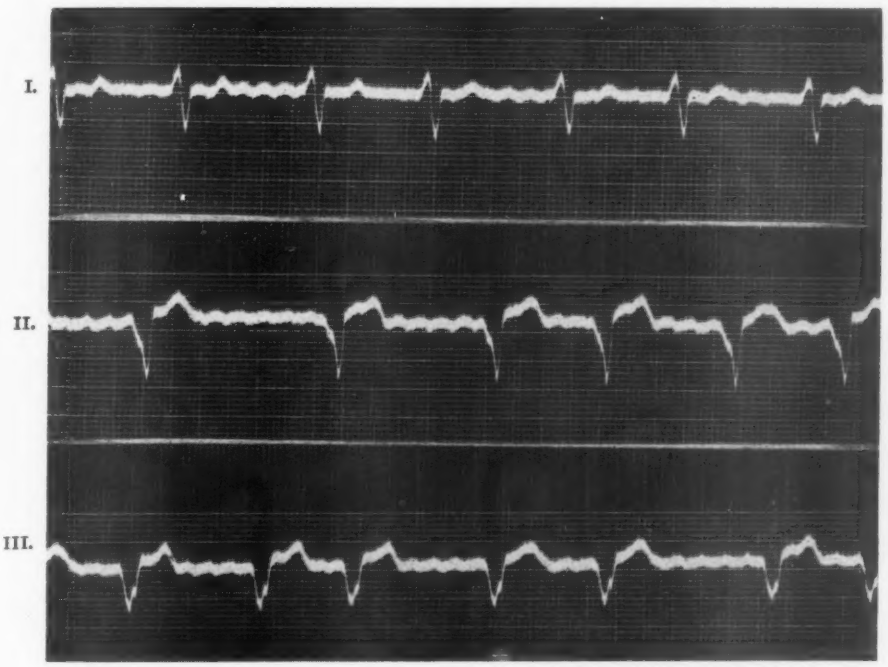

Fig. 3.—Aug. 26, 1943. Auricular fibrillation and right bundle branch block.

Nov. 4, 1943: The strips shown in Fig. 4 were selected from long tracings which were taken on this occasion. The auricular complexes were remarkable for the prominence of the auricular T waves. The P wave was upright in all leads. The auricular T wave was upright to slightly diphasic in Lead I, inverted in Leads II and III, and upright in Lead CF_1. In Lead III the auricular T wave was more prominent than the P wave. There was no displacement of the auricular S-T segment in the standard leads. It appeared slightly depressed, however, in Lead CF_1. The dominant rhythm was of normal sinus origin. In the accompanying figure, in Leads I*a*, II, and CF_1 there was delayed A-V conduction, with a P-R interval of about 0.44 second. Right bundle branch block was present. Lead I, strip *b*, showed incomplete A-V block with the Wenckebach phenomenon. The first complex after the dropped beat was a more nearly

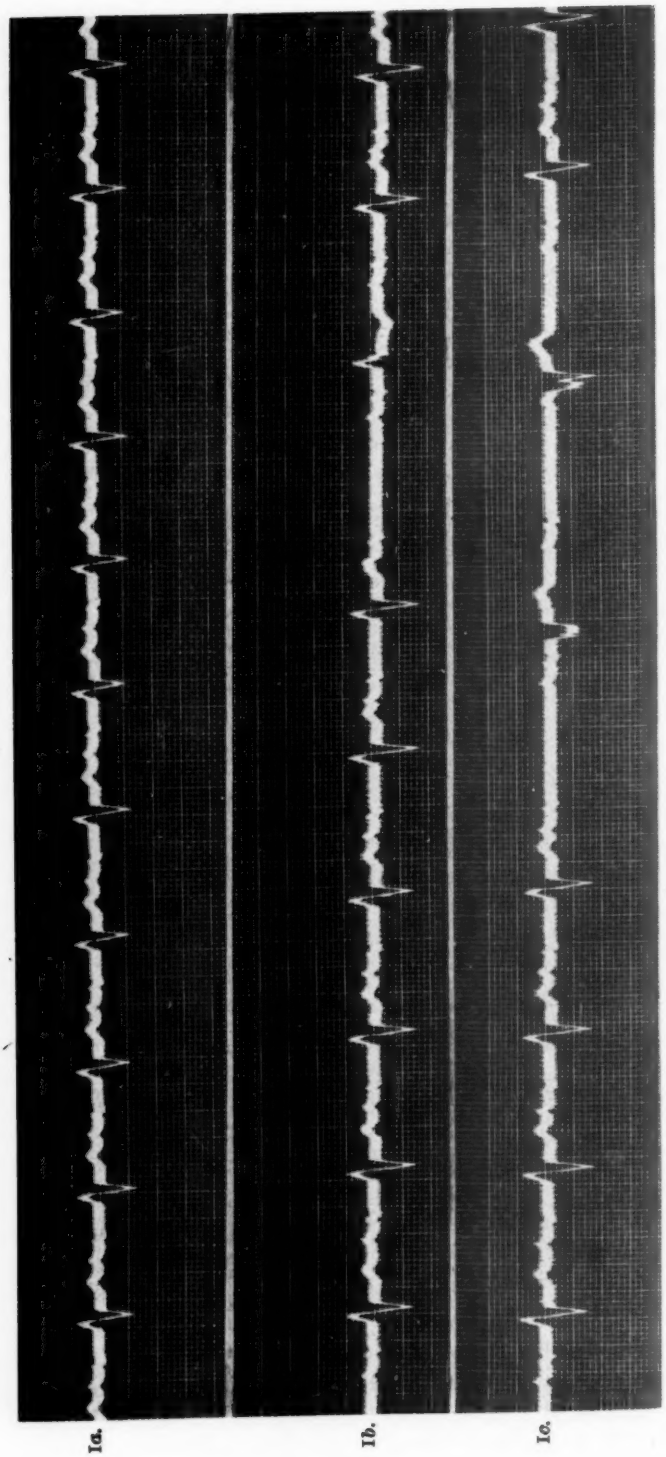

Fig. 4.—*(For legend see opposite page.)*

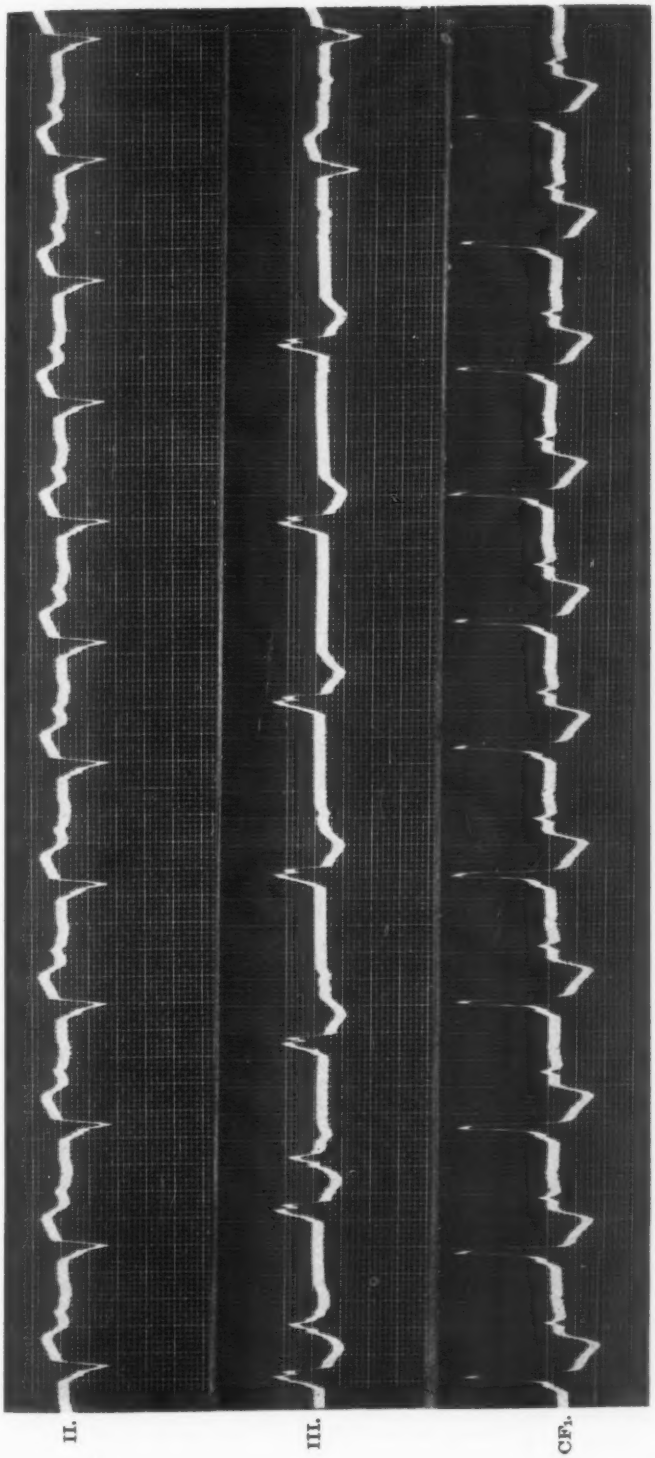

Fig. 4.—Nov. 4, 1943. Leads Ia, II, CF$_4$, regular sinus rhythm, prolonged A-V conduction time. Auricular T wave upright to diphasic in Lead Ia, inverted in Leads II and III, and upright in Lead CF$_4$. Lead Ib, incomplete A-V block with Wenckebach periods. First QRS complex after dropped beat shows improved intraventricular conduction. Lead Ic, incomplete A-V block, Wenckebach phenomenon, and A-V dissociation with idioventricular escape beats. Lead III, A-V nodal rhythm. First two nodal beats followed by premature ventricular contractions. Last two ventricular complexes are in response to sinus nodal impulses. Auricular T wave is inverted.

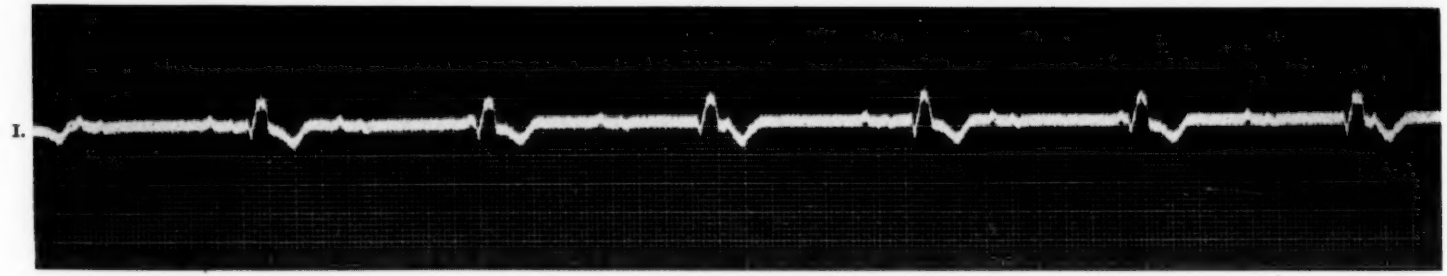

Fig. 5.—Nov. 23, 1943. Lead I. Complete A-V dissociation and left bundle branch block.

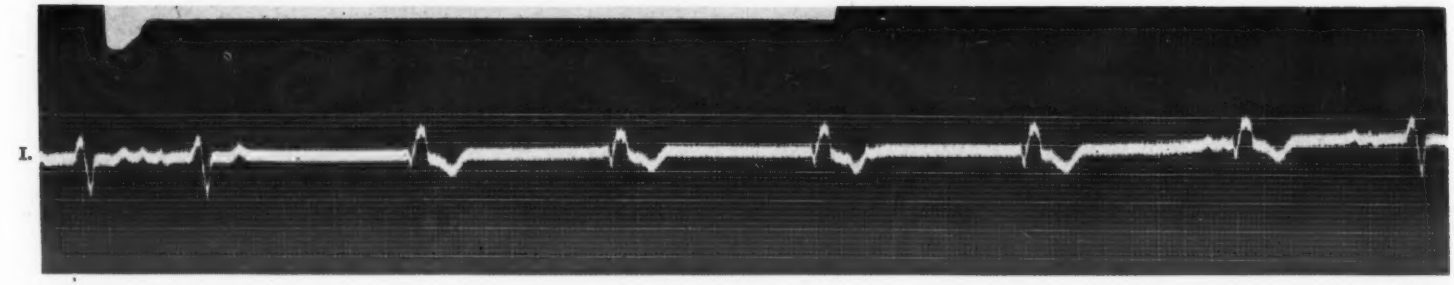

Fig. 6.—Nov. 23, 1943. Lead I. Regular sinus rhythm and right bundle branch block. Carotid sinus stimulation followed by A-V nodal rhythm with QRS complexes of left bundle branch block type.

normal ventricular complex than the others in the record. It indicated improved intraventricular conduction following the long pause due to the dropped beat.[4] Lead I, strip *c*, showed a short interlude of A-V dissociation with idioventricular escape beats. Lead III was of exceptional interest. During the first nine QRS complexes A-V nodal rhythm was present. The first two nodal beats were coupled with ventricular premature contractions which were interpolated. Retrograde P waves were seen clearly following the fourth, fifth, and sixth ventricular complexes after a delayed retrograde conduction time. When the sinus nodal pacemaker resumed command, the QRS complexes changed direction, indicating a change in intraventricular conduction.

Nov. 16, 1943: Regular sinus rhythm, first degree heart block, and right bundle branch block were present.

Nov. 18, 1943: Regular sinus rhythm, first degree A-V block, right bundle branch block, and premature ventricular contractions were present.

Nov. 23, 1943: There were present complete A-V block and left bundle branch block (Fig. 5, Lead I). Normal sinus rhythm and right bundle branch block appeared (Fig. 6, Lead I). After carotid sinus stimulation A-V nodal rhythm occurred, with ventricular responses of the left bundle branch block type.

Jan. 2, 1944: Regular sinus rhythm, first degree A-V block, and right bundle branch block were present. On this occasion multiple precordial leads were obtained. The auricular T wave became more prominent and upright in passing from the right to the left side of the heart.

Jan. 22, 1944: Regular sinus rhythm, first degree A-V block, and right bundle branch block were present. The A-V conduction time was only slightly shortened after intravenous administration of atropine sulfate (0.0012 mg.).

DISCUSSION

Following an attack of coronary occlusion this patient developed multiple disturbances of rhythm and conduction and an unusual auricular T-wave pattern. These features suggested the probability that infarction of the auricular myocardium had taken place. The following auricular mechanisms were recorded: Normal sinus rhythm, auricular flutter, auricular fibrillation, and A-V nodal rhythm. In addition there were premature ventricular contractions, paroxysmal ventricular tachycardia, and idioventricular escape beats. The conduction disturbances included first, second, and third degree A-V block and right and left bundle branch block. Certain aspects of these arrhythmias warrant special comment. The auricular flutter persisted for three years. It was not converted to fibrillation by digitalis, but after discontinuance of digitalis, conversion to fibrillation took place spontaneously. The combination of auricular flutter, and complete A-V heart block is, in itself, a rarity. Gray and Greenfield[5] in a recent review of the literature found only 31 reported cases and added one of their own. An unusual feature in our case was the presence of left bundle branch block during complete A-V block, and the shift to right bundle branch block when complete A-V block was not present. Fig. 4 was of interest because of the variety of forms of heart block encountered during one examination. Also of interest was the presence of nodal rhythm with

coupled premature ventricular systoles, an unusual form of bigeminy, and the presence of retrograde conduction of the impulse, with marked lengthening of the RP interval. The delayed A-V conduction was organic in origin. It did not disappear when digitalis was withdrawn, and it was not abolished by intravenous atropine sulfate. The carotid sinus was hypersensitive. Pressure on the right carotid sinus regularly produced A-V nodal rhythm, while left carotid pressure produced complete A-V block.

Probably the most interesting feature of this case was the unusually prominent auricular T wave. In Lead I this wave was upright to diphasic, with the upright deflection most prominent, and followed an upright P wave. In Leads II and III the auricular T wave was inverted. In the precordial leads the auricular T wave was upright. It was a fortunate coincidence that the P-R interval was lengthened so that the complete cycle of auricular activity was visible.

CONCLUSIONS

1. Following an attack of coronary occlusion multiple disturbances of rhythm and conduction and an unusual auricular T-wave pattern were seen.

2. These changes suggested that infarction of the auricular myocardium had occurred.

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TRANSIENT BUNDLE BRANCH BLOCK ASSOCIATED WITH TACHYCARDIA

LIEUTENANT HERBERT EICHERT, M.C., USNR

BUNDLE branch block, once established, tends to remain permanent. The exceptions, in which the block is temporary, have been described as intermittent, paroxysmal, or transient bundle branch block,* and a number of reviews of collected cases have been published. In most of the reported cases, the block occurred or persisted fortuitously and was not rigidly influenced by procedures carried out by the investigator. In a few instances, however, the observers noted that the block was affected by alterations of the cardiac rate. Such cases, in which the bundle branch block occurs only when the cardiac rate is rapid, are extremely rare. The case herein presented is an example of such a phenomenon. Comeau, Hamilton, and White,[1] who reviewed the largest series of cases of transient bundle branch block, stated that in the "routine records of their cases there was no constant correlation between cardiac rate and the degree of intraventricular conduction."[1]

Although bundle branch block, either transient or constant, is usually accompanied by other evidence of cardiovascular disease, the case of transient bundle branch block which will be presented is distinguished by the absence of other demonstrable cardiovascular abnormalities.

CASE HISTORY

R. F. W., a 29-year-old man, was hospitalized because of palpitation on exertion. During childhood he had a moderate number of "colds" and sore throats. His general health was otherwise always good and he does not recall having had any serious illnesses. There was no history of rheumatic fever, chorea, scarlet fever, diphtheria, or typhoid fever. Prior to entering the Navy in March, 1944, he was a foreman in a felt hat factory. Since this date he has been occupied principally as mess cook and stevedore in a Naval Construction Battalion. He smoked fifteen cigarettes and drank two cups of coffee daily. He did not use alcohol. His wife, his three children, his father, and one brother are living and well. His mother is said to be nervous and to suffer from sick headaches, fainting spells, and heart trouble. One sister is said to have died of tuberculosis of the spine, and one brother has "leakage of the heart."

Three years before admission to the hospital he noticed that severe physical exertion sometimes caused his heart to palpitate. At first this symptom rarely appeared but later such attacks of palpitation after exercise or violent excitement came more frequently and tended to last longer. Later still these attacks were accompanied by an aching feeling in the precordium. He became dizzy during the attacks, but never fainted.

At the time of his admission into the Navy in March, 1944, his resting pulse rate was recorded as 76 per minute. Two minutes after exercise the rate was recorded as 88 per

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*The term "transient bundle branch block," within the meaning of this article, bears no relationship to the Wolff-Parkinson-White syndrome of short P-R interval with prolonged QRS complex which has been referred to, although incorrectly, as "functional bundle branch block."

minute. His blood pressure was 150/60. It was also recorded at that time that he had a "functional heart murmur with a mild neurocirculatory disturbance."

During the previous year, and particularly during the previous three or four months, these attacks were both prolonged and severe because his work as a stevedore compelled him to do much heavy lifting. When he did not work hard he had few attacks. Invariably, however, after lying down and resting for five or ten minutes, the unpleasant sensations would gradually disappear as his heart slowed.

A review of the symptoms revealed that he had infrequent attacks of bilateral supraorbital headaches without nausea or vomiting. He also complained of intermittent mild, vague aches of the muscles. At times he experienced mild digestive disturbances such as abdominal distention and an uncomfortable feeling after eating; but these symptoms were never persistent or severe.

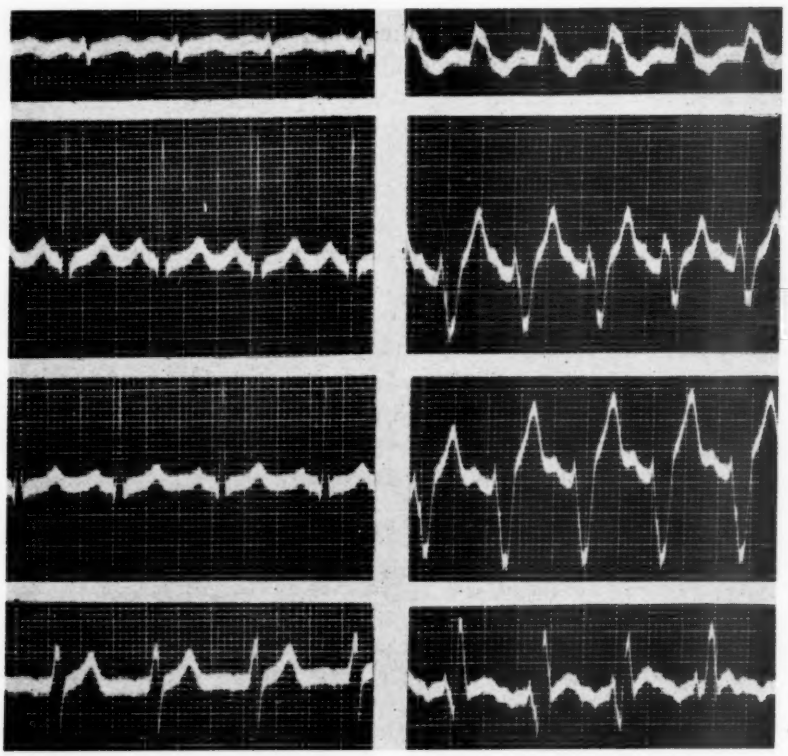


Fig. 1.—R. F. W., aged 29 years. Control (average rate 104 per minute) and bundle branch block following exercise (average rate about 135 per minute).

He was seen in consultation as an outpatient on Jan. 3, 1945. As he performed the Master two-step test,[2] it was observed that when his heart rate was rapid, a bundle branch block developed (Fig. 1); after he had rested for two minutes, this abnormality disappeared.

He was admitted to this hospital for observation on Jan. 8, 1945. He was of the asthenic type, being 69 inches in height and weighing 135 pounds. The resting blood pressure was 120/70. The resting pulse rate was 84 per minute and the respiratory rate was 22 per minute. The temperature was normal. He appeared to be somewhat anxious and ill at ease. His hands felt cold and he perspired moderately in the axillae. The examination of the eyes, including the eye grounds, revealed nothing significant. Small tonsillar tabs were present. His oral hygiene was poor. Several teeth were broken off at the gingival margins and others were carious.

The heart was not enlarged. No murmurs were heard and no abnormal accentuation or reduplication of cardiac sounds was noted; the heart rate and rhythm were normal. The veins were not engorged and there was no thickening of the peripheral arteries. Fluoroscopic examination of the heart indicated it to be normal in size, position, and contour. An x-ray of the chest showed no abnormalities (Fig. 3).

The blood Kahn was negative. The red blood count was 5,240,000 per cubic millimeter; hemoglobin, 14 Gm.; white blood count, 8,000 per cubic millimeter with a normal differential. The sedimentation rate was 11 mm. in one hour. The serum calcium determination was 10.7 mg. per cent and the blood nonprotein nitrogen was 27 mg. per cent. The concentration and dilution tests showed a range of 1.001 to 1.026 in the specific gravity of the urine. Stool studies were negative for enteric pathogens, ova, and parasites.

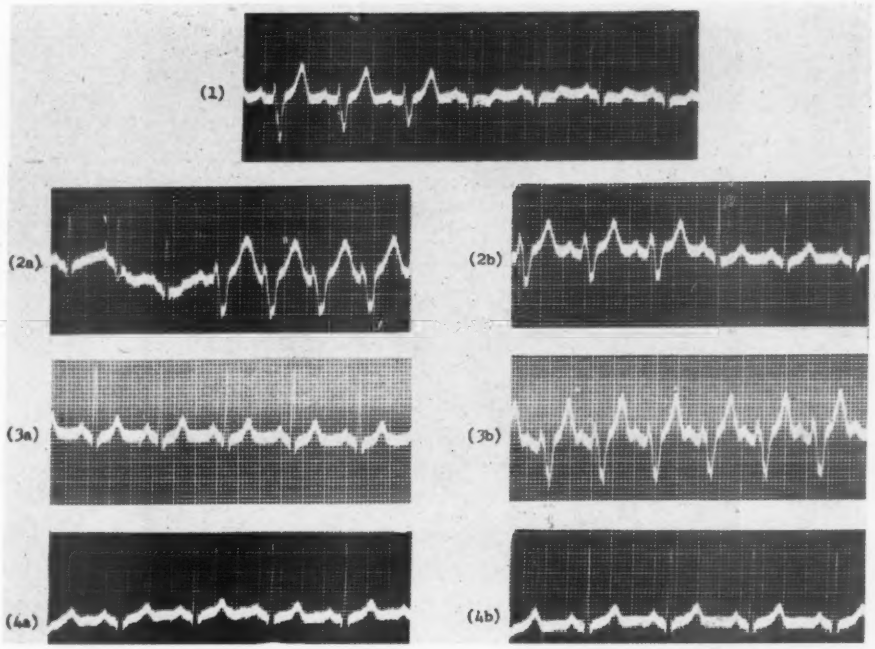


Fig. 2.—R. F. W., aged 29 years. Intermittent bundle branch block (Lead II). (*1*), Reversion to normal conduction when rate slowed following exercise. (*2*), After inhalation of amyl nitrite; interval between (*2a*) and (*2b*) about thirty seconds. (*3a*), Control; (*3b*), after 1/100 grain of atropine intravenously. (*4a*) Prostigmine followed by (*4b*) exercise; block did not develop.

Observations and Hospital Course.—Electrocardiograms taken before and after exercise showed that this patient had a normal intraventricular conduction time when the cardiac rate was relatively slow, but that he always developed bundle branch block when the rate increased above a critical level. The transition was invariably abrupt and the cycle marking the transition was of the same duration as the cycles preceding and following it.

By the use of the electrocardiograph and, later, the cardioscope it was found that the patient's subjective feeling of palpitation was usually a reliable indication of the presence of the bundle branch block. Although attacks of palpitation, and presumably block, occurred spontaneously, rarely was an electrocardiogram obtained during such spontaneous attacks. We therefore used various procedures to alter the heart rate so that the effect on the block of changes in rate could be studied.

Fig. 1 shows the appearance of block after the heart rate was increased by exercise.

Fig. 2 is a series of tracings all made on Lead II, which illustrate the effect of varia-

tion in rate induced in several ways. Fig. 2, (*1*), is a portion of tracing showing the transition from bundle branch block to normal conduction. The transition occurred as the heart rate was slowing following exercise. Fig. 2, (*2a*) and (*2b*), shows bundle branch block appearing after the inhalation of amyl nitrite. This tracing was a continuous one; a segment of thirty seconds' duration, between (*2a*) and (*2b*), was removed to facilitate illustration. Tracings (*3a*) and (*3b*) shown in Fig. 2 were taken before and after the intravenous injection of $\frac{1}{100}$ grain of atropine sulfate. This dose of atropine was not large enough to induce the block. The block appeared only after the patient assumed the upright position and hopped several times. Fig. 2, (*4a*), shows the effect of prostigmine. In this study the patient was given 1 c.c. of prostigmine methylsulfate 1:2,000 intramuscularly and was then exercised violently. Although he became dyspneic, his pulse rate did not increase markedly and bundle branch block did not develop.

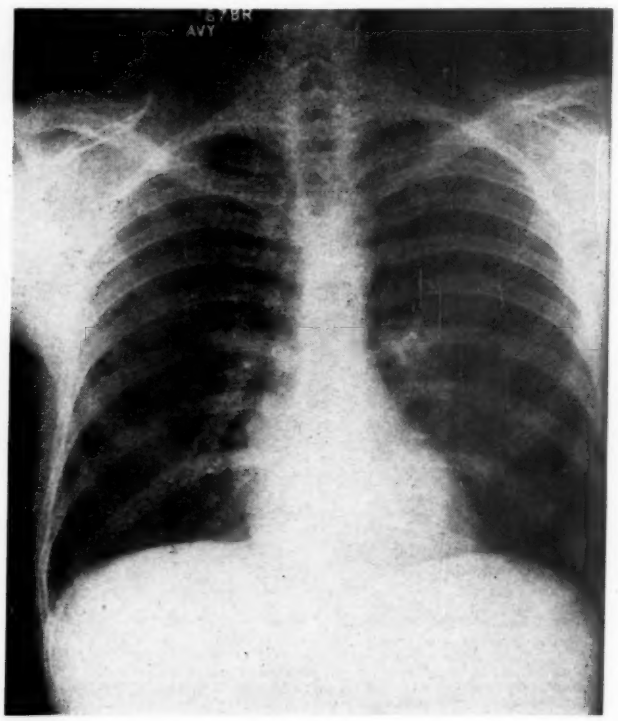


Fig. 3.

Several similar cases[1, 3] have been reported in which either carotid sinus pressure or oxygen inhalation reduced the heart rate and caused bundle branch block to disappear. Since rapid heart rates could be maintained in this patient only under artificial conditions it was decided to attempt to maintain a high rate by atropine administration and then to observe the effects of oxygen and of carotid sinus pressure upon the block. Atropine sulfate, $\frac{1}{50}$ grain, administered intravenously, increased the rate to a point where the block occurred transiently, but it could not be maintained. However, when the patient stood erect, the rate rose to 136 per minute and the block appeared and persisted. He was then given 100 per cent oxygen inhalation for five minutes. There was neither marked slowing of the rate nor alteration in the degree of block. The application of carotid sinus pressure first on one side, then on the other, and finally bilaterally, was likewise ineffective in altering either the rate or the contour of the complexes.

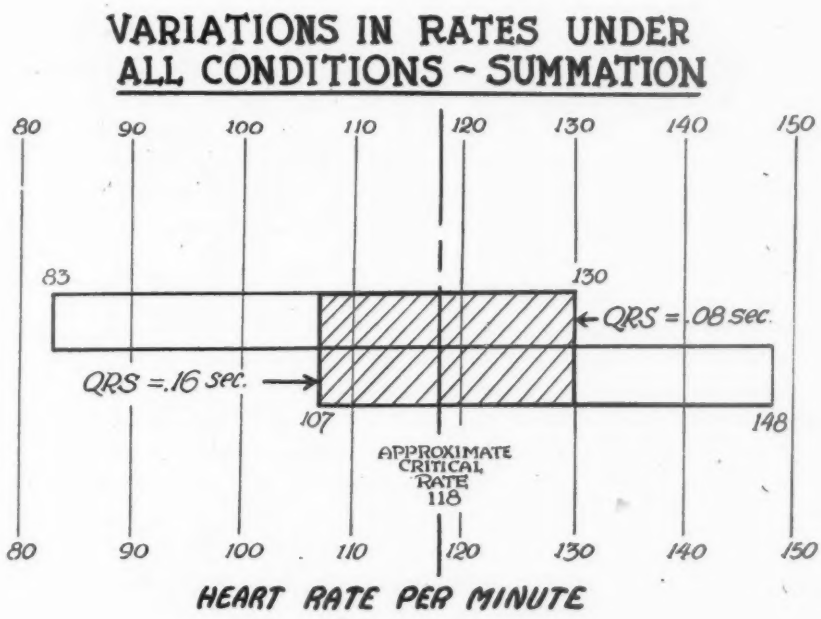
Table I shows the observed variations in rate and the appearance of block under various conditions. Table II is a summary of all the observed variations in rates under different experimental conditions and of the rates at which bundle branch block was observed. The rate of 118 per minute, the average rate at which the transition from normal conduction to bundle branch block occurred, is the approximate "critical rate." It should be noted that occasionally a rate higher than the "cortical rate" was necessary to induce the block. Also, the rate sometimes went below the critical level before the block disappeared.

During the time spent in the hospital, the patient led a quiet existence devoid of strenuous physical activity. His attacks of palpitation became less frequent, and, at the time of his evacuation to a mainland hospital, he was feeling relatively well.

TABLE I. VARIATIONS IN RATE AND DEVELOPMENT OF BUNDLE BRANCH BLOCK UNDER VARIOUS EXPERIMENTAL PROCEDURES

PROCEDURE	0.08 SEC. MIN.-MAX.	0.16 SEC. MIN.-MAX.
Resting	83-100	107-115
Immediately after exercise		107-126
Two minutes after 2-step exercise	83- 85	
Atropine sulfate, 1/100 grain intravenously	107-110	
Atropine, 1/100 grain and light exercise		107-146
Atropine, 1/100 grain patient standing		135-148
Atropine, 1/100 grain patient bending over	92- 96	
Amyl nitrite inhalation	98-130	107-136
Carotid sinus pressure bilateral, patient reclining	84- 86	
Adrenalin, 1 c.c. intramuscularly	90-112	

TABLE II.



DISCUSSION

The lability of the cardiac conduction mechanism in this case offered an unusual opportunity to observe the function of the heart during periods of normal and prolonged intraventricular conduction time. Such observations

have a possible bearing on the existing concepts of the etiology and mechanism of bundle branch block.

The preponderant opinion concerning the etiology of bundle branch block is expressed in the literature by the statements that "bundle branch block is a manifestation of advanced cardiovascular disease" and that the "electrocardiographic changes must be attributed to anoxemia of the conducting tissues."[1] In most of the cases of bundle branch block in which the etiological factors could be established, the patients were found to have hypertensive or arteriosclerotic coronary artery disease.[4] In such cases it is believed that an arteriosclerotic narrowing of a coronary artery branch supplying the bundle results in anoxia, with eventual fibrosis. As one would expect, most persons who have bundle branch block are in the higher age groups. The youngest case in the series reported by Comeau and his co-workers[1] was found in a patient 38 years of age.

The subject of this report experienced his first symptoms at 26 years of age. Our investigations revealed none of the usual stigmata of hypertensive or arteriosclerotic cardiovascular disease. All blood pressure readings as well as the renal function tests were within normal limits. There was no evidence of the existence of cardiac insufficiency or failure. In spite of the development of bundle branch block during the test, the exercise tolerance was good. Observation of the fundal vessels and palpation of the peripheral vessels showed the arteries to be normal.

In one of the cases cited[3] the administration of oxygen during a period of bundle branch block caused the QRS to revert to normal. This response to oxygen therapy was considered to support the concept that the block was caused by anoxia of the bundle. Administration of oxygen to our patient during a period of bundle branch block had no observable effect. In several other cases cited in substantiation of the anoxic theory of bundle branch block, the inhalation of amyl nitrite caused the block to disappear. In our case the inhalation of amyl nitrite invariably brought about bundle branch block whenever the "critical rate" was exceeded.

Other diseases have been mentioned as etiological factors in the occurrence of bundle branch block. These include chronic rheumatic heart diseases and acute infections, neither of which could be demonstrated in our patient.

Vagal influences are known to produce varying degrees of block of the S-A or A-V node. Stimulation of vagus reflexes by carotid sinus pressure had no apparent effect on cardiac conduction in this subject. On the contrary, increase in vagal tone brought about by the administration of prostigmine prevented the development of block by its depressant effect on the cardiac rate.

Congenital defects of the conduction system have been mentioned as possible causes of similar abnormalities. None of the features of this case enabled us to establish this possibility.

A case cited by Graybiel and his co-workers[3] had more features in common with this case than any other case reviewed. Their patient, a 24-year-old "healthy" aviator, developed transient bundle branch block as a result of a

fright stimulus. The firing of a pistol close to him caused the block to develop; it persisted for about two days. From their observations in that case and in others among young men in whom the QRS duration was abnormally prolonged, the authors suggested that "possibly all the disturbances of intraventricular conduction need not be explained on an anatomic basis."

Many controversial theories have recently been offered to explain the mechanism of bundle branch block. During the investigation of our case, we were able to test the validity of some of these theories by determining whether or not they conformed to the conditions that follow. We obtained many graphic records of the transition between normal conduction and bundle branch block. The following characteristics were repeatedly recorded: (1) Bundle branch block always occurred when the cardiac rate exceeded a certain level, and the duration of the QRS complex always became normal when the rate decreased to normal levels. (2) Any stimulus which caused the rate to increase sufficiently produced the block. (3) The transition always occurred abruptly: the cycle in which the first bundle branch block complex appeared approximated the lengths of the cycles occurring immediately before and after the transition cycle. (4) The increase or decrease in the QRS duration was not gradual, but occurred instantly during the transition cycle. (5) There was an immediate reversal of axis deviation at the time the block occurred. (6) During the period of observation, the block showed no tendency to become permanent.

Comeau and his co-workers[1] explain the abrupt changes of the QRS complexes in transient bundle branch block by assuming that conduction in the bundle is not completely blocked but simply depressed. Under such conditions, an increase in the frequency of the impulses transmitted results in an increase in the degree of conduction depression, until at the critical level an impulse traveling the roundabout way through the intact side and the myocardium reaches the affected ventricle before the impulse descending through the depressed branch is able to do so. The slow impulse reaches the ventricle too late to participate in its activation and is as ineffective as an impulse which is completely blocked. Thus small changes "such as an increase or decrease in diastolic rest due to alterations in heart rate" might produce the abrupt changes in the form of the complexes.

This concept, however, fails to consider the possibility that at the approximate critical rate, two impulses might reach different points of the affected ventricle at the same instant. This could occur if one impulse reaches the affected ventricle by traversing the normally functioning bundle branch while the impulse passed through the depressed bundle. Until one impulse comes to reach the ventricle sufficiently early to completely overshadow the effect of the slower impulse, one would expect to find records showing complexes of an intermediate form. Such complexes were recorded in a case of bundle branch block reported by Miller and Fulton.[7] In that case, several electrocardiographic records showed gradual alterations of the normal complexes which resulted eventually in the typical bundle branch complex. In the case herein reported intermediate complexes were never noted.

This hypothesis of depressed conduction through the bundle branch system has been weakened further by recent studies of the cardiac conduction system. Glomset, Glomset, and Birge,[5] after painstaking study, were unable to demonstrate a readily recognizable and anatomically distinct ventricular conduction system. Failing to find a specific conduction system, they postulated that bundle branch block complexes are a result of unilateral ventricular strain, or unilateral coronary insufficiency, or a combination of the two. This concept is somewhat in accord with that of Master, Kalter, Dack, and Jaffe,[6] who believe that the bundle branch complex results from a disproportionate enlargement of one or the other ventricle. Since ventricular strain and enlargement develop gradually, the contour of the QRS complex in transient bundle branch block would be expected to change gradually if bundle branch block is the result of these changes.

These hypotheses therefore seem unsatisfactory explanations of the abrupt changes in the QRS complexes noted in this and other similar cases. It would appear that a better explanation of the change of the QRS complex in transient bundle branch block must await the results of further investigation.

SUMMARY

1. An unusual case of transient bundle branch block is presented in which normal QRS complexes were present at slow cardiac rates and bundle branch block appeared at higher rates; this alteration occurred whenever the rate was varied sufficiently.

2. No demonstrable evidence of organic heart disease could be found to account for the transient block.

3. Theories of etiology and the mechanics of bundle branch block are discussed in relationship to this case.

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Abstracts and Reviews

Selected Abstracts

Blalock, A.: Physiopathology and Surgical Treatment of Congenital Cardiovascular Defects. Bull. New York Acad. Med. 22: 57 (Feb.) 1946.

The subject of congenital cardiovascular defects in which surgical treatment has been effective is presented as the Harvey Lecture. The author reports his experiences with operative procedures in the treatment of patent ductus arteriosus, coarctation of the aorta, and pulmonary stenosis and atresia. The operation for pulmonary stenosis and atresia is of particular interest. As recently performed, it usually consists of anastomosis of the right subclavian artery and the pulmonary artery. The left subclavian artery is seldom used because considerable kinking of the vessel occurs when the anastomosis is made. In infants and small children, the innominate artery should be used. Another consideration in the choice of which artery to use is the occurrence of a right rather than a normal left aortic arch. When the aorta descends on the right, the innominate artery is directed to the left and must be approached through the left side of the chest. There have been 16 patients of this type in the author's series. The correct diagnosis was made before operation by fluoroscopic examination in which deviation of the barium-filled esophagus was seen.

The author stresses the importance of making a direct measurement of the pressure in the pulmonary artery when the vessel is exposed preparatory to the anastomosis. In most of his patients the pulmonary arterial pressure was approximately 175 mm. of water. In one patient who had a pressure of 310 mm. of water, the operation was performed but the cyanosis did not disappear and death occurred on the twenty-fourth postoperative day. At autopsy, a single ventricle was found, from which both the aorta and the pulmonary artery arose. There was little if any pulmonary stenosis. The cyanosis in this case was due to complete absence of a ventricular septum. It was obvious that the anastomosis should not have been performed. Recognition of the high pressure in the pulmonary artery should have furnished the clue to the true nature of the condition.

There was no significant impairment of the circulation in the arm when the subclavian artery was divided and used for the anastomosis. Although the skin temperature of the limb on the operated side was slightly cooler, motion and sensation were little, if at all, affected.

Either the right or left subclavian was used for the anastomosis in 26 patients. In 23 additional patients the innominate artery was used and in each instance it was necessary to ligate the first portion of the subclavian artery. The first portion of the right or left subclavian artery was therefore ligated in 49 cases, and in none of these was there any evidence of dangerous interference with the circulation of the arm. Seven patients died. In two of the seven patients the preoperative diagnosis was incorrect. In two of the remaining five cases death was attributed to cerebral ischemia or thrombosis.

The author's results up to Nov. 1, 1945, are summarized as follows: Fifty-seven operations have been performed on 55 patients. Ten of these patients have died. In this group the preoperative diagnosis, tetralogy of Fallot, was proved by autopsy to be in error in two instances. If these two cases in which the diagnosis was incorrect are excluded, there were eight deaths among the remaining 50 patients, a mortality of 16 per cent. In 40 of the living patients, improvement has been conspicuous. The condition of most of the children has been altered from invalidism to apparent if not real normality. The cyanosis has largely disappeared, even after moderate effort. The clubbing of fingers has either disappeared or con-

siderably diminished. The average oxygen saturation of arterial blood has risen from 49 per cent prior to operation to 79 per cent two to three weeks after operation.

It is emphasized that the operation is not of value to all patients who have persistent cyanosis. It is indicated only in those malformations in which the cardinal difficulty is lack of adequate circulation to the lungs. BELLET.

Silver, S. L., and Baker, L. A.: Reexamination of Veterans Discharged Because of Heart Disease or Hypertension. J. A. M. A. 130: 136 (Jan. 19) 1946.

Five hundred World War II veterans who had been discharged from the Armed Services because of diagnoses referable to the cardiovascular system, were re-examined and their medical records were reviewed. In 111 cases, the diagnosis of cardiovascular disease for which the patient received his certificate of disability discharge was not confirmed. In the remaining 389 patients whose diagnoses were confirmed, rheumatic heart disease had the highest frequency with an incidence of 169 cases (43.4 per cent). Of this group the mitral valve was involved in 82.6 per cent, the aortic valve was involved in 40.8 per cent, and mitral stenosis was present in 47.3 per cent. Arterial hypertension was the second most common diagnosis and occurred in 86 (27.5 per cent) of the patients. Thirty-three patients had been discharged because of coronary disease and of these, 21 patients had acute myocardial infarction. Congenital and syphilitic cardiovascular diseases were rare.

In 46 of the patients who had cardiovascular disease, no definite etiological factor could be established. The authors noted a conspicuous tendency for the signs of neurocirculatory asthenia and hypertension to disappear following return to civilian environment, indicating that poor psychologic adjustment to military life had been responsible for the transient clinical manifestations. In about 40 per cent of this series there was a history of an etiological factor, or symptoms referable to the heart, or abnormal physical findings, which antedated entry into the service. It is pointed out that a more careful history and examination might have eliminated this group before induction. BELLET.

Logue, R. B., and Mullins, F.: Polyarteritis Nodosa: Report of 11 Cases With Review of Recent Literature. Ann. Int. Med. 24: 11 (Jan.) 1946.

The authors report 11 cases of polyarteritis nodosa diagnosed during life and review 177 cases reported in the English literature up to 1942. Polyarteritis nodosa affects men more frequently than women; in the authors' series there were 10 men and 1 woman. The ages of the patients ranged from 15 to 65 years. The duration of the illness varied from two and one-half months to one year, with recovery in one patient, who was well two years after onset of the disease. Hypertension was present in every patient at some time during the course of the disease. Leucocytosis occurred in all patients and eosinophilia was present in five patients. In three cases the diagnosis was made by laparotomy. One patient developed a perirenal hemorrhage, and nephrectomy was performed because of a suspected neoplasm. Four patients had clinical and pathologic manifestations of involvement of the coronary arteries with progressive electrocardiographic evidence of coronary insufficiency. Three patients showed clinical or pathologic evidence of involvement of the testicular arteries. NAIDE.

Russi, S., Blumenthal, H. T., and Gray, S. H.: Small Adenomas of the Adrenal Cortex in Hypertension and Diabetes. Arch. Int. Med. 76: 284 (Nov.-Dec.) 1945.

The incidence of benign adenomas of the adrenal cortex in 9,000 routine autopsies was found to be at least 1.45 per cent. The incidence was 2 per cent in women and 1.2 per cent in men. Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general autopsy group, and both diseases were frequently present in association with such a tumor in a single person.

The authors discuss the relation of the adrenal hormones to diabetes and hypertension. In relation to hypertension the authors believe that there is a direct effect of the cortical hormones on vascular tone, the hormones rendering a person more sensitive to renin. NAIDE.

Naide, M., and Sayen, A.: Venospasm: Its Part in Producing the Clinical Picture of Raynaud's Disease. Arch. Int. Med. 77: 16 (Jan.) 1946.

Observation of 10 patients with Raynaud's disease and four patients with Raynaud's phenomenon has disclosed evidence that spasm of the veins as well as of the arteries is present in the majority of these patients. Arterial spasm alone cannot explain the clinical picture in most patients. In some patients venospasm may predominate over arterial spasm. The clinical features vary in each patient depending on which part of the vascular tree is predominantly involved in the abnormal vasoconstriction. It is suggested that in some patients with Raynaud's disease the clinical picture is influenced by an anatomic disproportion in capacity between arterial and venous flow. On the basis of clinical observations of these patients during the test for basal vascular tone, a classification has been made to clarify the terms Raynaud's disease and Raynaud's phenomenon. Raynaud's disease is not rare. The milder forms are fairly common and do not deserve the serious connotation usually associated with the diagnosis. Reassurance is an important part of treatment. A patient with so-called "cold allergy" was found to develop venospasm on exposure to cold without developing arterial constriction, which explained the development of cyanosis and marked swelling without blanching. AUTHORS.

Peet, M. M., and Isberg, E. M.: The Surgical Treatment of Arterial Hypertension. J. A. M. A. 130: 467 (Feb. 23) 1946.

Since the first bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy was performed by Peet in 1933, more than 1,500 patients with essential hypertension have received this treatment at the Hospital of the University of Michigan. The authors report the results of this treatment in 437 patients followed for five to twelve years. Two hundred and fifty-one patients, or 57.5 per cent of the series, were living five to eleven years after operation. At the end of five postoperative years 64.8 per cent of the entire series were alive. The hypertensive state in 82 per cent of the patients in this series had already progressed to serious organic disease prior to operation. Fifty-six per cent of all the men had died, while the mortality among the women was only 30 per cent. Ninety-five per cent of hypertensive patients who showed no preoperative evidence of cardiac, cerebrovascular, or renal involvement were living five to eleven years after operation.

Approximately one-third of all patients who manifested preoperative evidence of organic heart disease, cerebrovascular disease, or impaired kidney function did not survive five to eleven years. Nineteen per cent of 112 patients with preoperative malignant hypertension were living five to eleven years later.

Fifty-one patients had maintained normal blood pressure levels and 28 showed no evidence whatever of hypertensive disease five to eleven years after operation. Significant reductions in blood pressure, complete and definite symptomatic relief, improvement of eye grounds, and improvement of abnormal electrocardiograms, cardiac enlargement, and kidney concentrating ability had been maintained for five to eleven postoperative years in a remarkable percentage of patients. Sixty per cent of patients who had previous cerebral accidents suffered no recurrence during the long postoperative period.

Surgical treatment is a measure to be considered in the management of every case of essential hypertension but to be utilized only when indicated. Evidence of progression and activity of hypertensive disease constitutes indication for surgical treatment. NAIDE.

Loewe, L., Rosenblatt, P., and Hirsch, E.: Venous Thromboembolic Disease. J. A. M. A. 130: 386 (Feb. 16) 1946.

One hundred and twenty-five cases of thrombophlebitis and/or phlebothrombosis treated by the subcutaneous administration of heparin in the Pitkin menstruum are reported. Pitkin's menstruum consists of 18 per cent gelatin, 8 per cent dextrose, 0.5 per cent glacial acetic acid, and sufficient distilled water to make 100 per cent. Each ampule contains 200

mg. of heparin/Pitkin menstruum. The average patient can be kept heparinized by the administration of 300 mg. every second day. The usual period of treatment for the average case of thrombophlebitis is ten days to two weeks.

The treatment of venous thromboembolic disease with subcutaneous heparin in this manner was attended with lessened morbidity, prompt and rapid clinical improvement, and little or no residual edema. Treatment failures with other methods have subsequently ended in recovery following the routine administration of heparin in the Pitkin menstruum. The authors recommend this method of treating venous thromboembolic disease as being safe, simple, practical, and effective. NAIDE.

Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis. J. A. M. A. 130: 398 (Feb. 16) 1946.

The authors studied the use of dicumarol as an anticoagulant in 110 patients with coronary thrombosis and myocardial infarction. Sixty patients received the usual treatment, while 50 received in addition dicumarol sufficient to maintain their plasma prothrombin activity at 35 to 50 per cent of normal. It was noted that three of every four cases of coronary thrombosis exhibited an increased prothrombin activity with increased clotting tendency. In view of this increased clotting tendency and due to the formation of mural thrombi and the danger of emboli, the anticoagulant seemed indicated to prevent the occurrence of such complications. It is also suggested that the administration of adequate amounts of an anticoagulant may prevent extension of the thrombus and reduce chances of future formation of mural thrombi or venous thromboses in the lower part of the body.

Dicumarol was administered to the 50 patients with coronary occlusion throughout their hospital course, which averaged forty-two days. Aside from a mild diarrhea and occasional nausea or headaches, no toxic effects were observed. No case of frank hemorrhage and no deaths ascribable to dicumarol occurred in this series. It was noted that the sedimentation time was increased by the drug to such an extent that it no longer served as an index of healing in the damaged myocardium.

Contraindications to dicumarol administration include renal disease, evident hepatic disease, or a blood dyscrasia with hemorrhagic tendencies. Patients with definite hypertension must be carefully observed from the standpoint of regulation of dosage.

The incidence of clinical embolism was 16 per cent in the group not receiving dicumarol and 2 per cent in the dicumarolized group. The mortality rate was 20 per cent in the nondicumarolized group and 4 per cent in the dicumarolized group. There was no evidence of more rapid healing of the infarction as judged by the electrocardiograms of the two groups.

In view of the recent reports that digitalis tends to increase the tendency toward coagulation the authors particularly advocate the use of dicumarol in patients with coronary thrombosis who are receiving digitalis.

In view of the encouraging results, it is suggested that further clinical evaluation of dicumarol is warranted. BELLET.

Spain, D. M., and Handler, B. J.: Chronic Cor Pulmonale. Arch. Int. Med. 77: 1 (Jan.) 1946.

The subject of chronic cor pulmonale is discussed from the standpoint of incidence, etiology, pathogenesis, clinical picture, diagnosis, clinical course, and treatment. This report is based upon a series of 60 consecutive cases of cor pulmonale studied at necropsy. Those cases were selected in which there was no significant evidence of hypertension, valvular heart disease, congenital lesion, syphilitic cardiovascular disease, or coronary atherosclerosis and at necropsy the wall of the right ventricle was found to be hypertrophied to a greater degree than that of the left ventricle. The following underlying pulmonary conditions were present in this series: emphysema in 40 cases (66 per cent);

bronchiectasis and bronchial asthma, each in six cases; silicotuberculosis in three cases; pulmonary tuberculosis in two cases; and kyphoscoliosis, pulmonary arteriolarsclerosis, and organized pulmonary thrombi, each in one case. The role and method by which each of these conditions acts in producing cor pulmonale is discussed in detail.

The authors emphasize the common errors made clinically in the diagnosis of this condition. In about 50 per cent of the cases the common error was to denote arteriosclerotic heart disease. They emphasize the following points in making a correct diagnosis: careful observation of physical signs, increase in size of the heart toward the right, prominence of impulse in the epigastrium, accentuation of pulmonic second sounds, roentgenographic and fluoroscopic studies, and presence of right axis deviation in the electrocardiogram. Occasionally in the presence of congestive failure, murmurs appearing over the pulmonic area give rise to an erroneous diagnosis of rheumatic or congenital heart disease. BELLET.

Rosenberg, D. H.: Acute Myocarditis in Mumps (Epidemic Parotitis). Arch. Int. Med. 76: 257 (Nov.-Dec.) 1945.

Cardiac involvement in mumps has been previously considered rare. Rosenberg observed significant electrocardiographic evidence of myocardial involvement in 16 of 104 patients studied (15.4 per cent). The following electrocardiographic abnormalities were encountered: biphasic or inverted P waves in one or more leads, prolongation of the P-R interval, elevation of the S-T segment in CF_4, and inversion of the T waves. Alterations of the T waves were observed in all 16 patients and occurred with the same frequency in each of the four leads. In this series there were also two cases of high-grade A-V heart block; one complete, the other partial. In all but one patient, electrocardiographic abnormalities were observed between the fifth and tenth days of illness and, in the majority of patients, were present on the eighth or ninth days. Precordial pain, either alone or with dyspnea, and palpitation developed in four of the 16 patients.

The nature of the histopathologic changes in the myocardium has not been definitely determined. It is not certain whether they represent an acute interstitial myocarditis with infiltration of polymorphonuclear leucocytes, as reported in the single case of Manca, or other milder types of myocardial involvement. From the clinical course and electrocardiographic findings, it is suggested that the myocardial changes are usually mild and reversible. The author makes the additional point that since the parotid involvement in mumps is not infrequently slight, and often overlooked in spite of the other clinical manifestations of the disease, the presence of arthralgia in such cases, together with electrocardiographic changes, might lead to a mistaken diagnosis of rheumatic fever. These observations cast further doubt on the specificity of the delay in A-V conduction time in the diagnosis of rheumatic fever. BELLET.

del Solar, A., Dussaillant, G., Brodsky, M., and Levy, M.: A Critical Study of the Medical Treatment of Arterial Hypertension. Rev. méd. de Chile 73: 293 (April) 1945.

A study was made of the effectiveness of various forms of medical treatment for hypertension. A series of 182 cooperative patients who had essential hypertension was observed over a period of several years. The patients were all ambulatory and their blood pressures averaged 160 to 220 mm., systolic, and 90 to 130 mm., diastolic. They were examined at intervals of one to two weeks under rigidly consistent circumstances. Each patient was given a placebo for several months. This was followed by administration of one of the active drugs to be tested, also for several months. Finally a terminal placebo was given. For each patient, a determination was made of the independent blood pressure, which was the average blood pressure for the period in which no active medication was taken.

The administration of placebos was accompanied by a significant fall of systolic pressure in relation to the independent blood pressure in 13.9 per cent ± 3.2 and of diastolic pressure in 8.7 per cent ± 2.6 of 115 cases. Symptoms were alleviated in 83 per cent. These effects were

apparently due solely to psychogenic factors. Potassium thiocyanate, administered to 26 patients, produced a significant fall of systolic pressure in relation to the independent blood pressure in 73.1 per cent ± 8.7 and of the diastolic pressure in 69.2 per cent ± 9. The difference between the effect of thiocyanate and that of the placebo was too great to have been due to chance and thiocyanate is thereby demonstrated conclusively to have a marked hypotensive action. Other drugs tested, however, including bismuth subnitrate, sodium nitrite, bromide-phenobarbital, potassium iodide, and diethylstilbestrol, were devoid of any demonstrable action in lowering blood pressure with respect to the independent pressure. LAPLACE.

Warembourg, H., and Fontan, M.: Considerations of Cardiac Reaction to Right and Left Pneumothorax. L'Echo Med. du Nord **15**: 685 (Dec.) 1944.

The cardiac reactions to pneumothorax were studied over a period of several years to determine whether there are any differences characteristic of one side as compared with the other.

Left-sided pneumothorax produced no special clinical reactions of the heart, and serious accidents were rare. The heart rate was occasionally accelerated but sometimes was slowed. Radiologically, the heart was shifted to the right. Termination of pneumothorax was often followed by functional disorders of the heart which were benign but troublesome and included precordial pain, palpitation, and tachycardia. Torsion of the heart was sometimes accompanied by a loud systolic murmur at the pulmonic area. The changes in the electrocardiogram following left-sided pneumothorax included right axis deviation (34 per cent), deep Q wave (29 per cent), and alteration of T waves (33 per cent).

Right-sided pneumothorax was accompanied by transient acceleration of heart rate and never by slowing. All of the significant arrhythmias which were encountered, such as extrasystoles and paroxysmal tachycardia occurred when pneumothorax was on the right. In general, however, right pneumothorax did not cause the functional disorders of pneumothorax on the left. Right axis deviation and deviation of the S-T intervals occurred more frequently with right than with left pneumothorax and a tendency to low voltage was often manifested. LAPLACE.

Prinzmetal, M., and Bergman, H. C.: The Nature of the Circulatory Changes in Burn Shock. Clin. Sc. **5**: 205, 1945.

When rats were burned at 100° C. for fifteen seconds, denervation did not change the mortality or survival time. The shock produced by this type of burn is not explained by the small volume of local fluid loss and must therefore be toxic (humoral) in origin. The degree of hemoconcentration did not indicate the severity of this type of shock since there was insufficient local fluid loss to cause a significant elevation of hemoglobin. In toxic burn shock the hemoglobin values may fall and anemia may occur due partly to transfer of fluid from the tissues into the blood vessels and probably also to retention of red blood cells in the capillaries.

The characteristics of toxic burn shock are demonstrated histologically to include an increase in the number of open capillaries and in the amount of blood retained in each capillary. The primary disturbance is capillary atony, visceral congestion, and diminution of bleeding volume which occur within one minute after burns. The vascular disturbance which prevents vascular contraction causes the organs of the exsanguinated shocked animals to remain congested while those of the exsanguinated normal animals become pale. Impairment of contractile power of the peripheral circulation in shock with consequent reduction in venous return, was demonstrated by the fact that the bleeding volume of animals without hearts was the same as those with hearts. A humoral agent in the blood of burned animals can be demonstrated by the reduction of the bleeding volume of normal animals after they have been injected with large amounts of blood from burned animals. LAPLACE.

Lewis, T.: Congenital Tricuspid Stenosis. Clin. Sc. 5: 261, 1945.

A case of tricuspid stenosis in a newly born child is described. The macroscopic appearance was that of endocarditis, but on histologic examination it was found that the lesion was a congenital malformation. Valvular deformities discovered in early life are believed to be usually if not always the result of congenital malformation rather than endocarditis. LAPLACE.

Pickering, G. W., and Sanderson, P. H.: Angina Pectoris and Tobacco. Clin. Sc. 5: 275, 1945.

Tobacco angina is regarded by the authors as rare in occurrence but important because of its implications that tobacco may cause constriction of the coronary arteries. Three cases are reported in which anginal pain was induced or aggravated by smoking. One of the patients was carefully studied with respect to the manner in which smoking produced the pain. When the patient smoked following the disappearance of pain produced by exercise, the pain reappeared. It reappeared, however, only if smoking was accompanied by an adequate increase in pulse rate. Exercise tolerance was not reduced by smoking before or during the exercise. Smoking was therefore a relatively minor factor in the production of anginal pain in this case, and it appeared to produce the pain by increasing the work of the heart rather than by causing vasoconstriction.

It is pointed out that use of the term "tobacco angina" is scarcely justifiable since smoking plays such a relatively small and inconsequential part in the production of anginal pain. LAPLACE.

Eyster, J. A. E., and Gilson, W. E.: The Development and Contour of Cardiac Injury Potential. Am. J. Physiol. 145: 507 (Feb.) 1946.

By applying increasing increments of suction to a small region of heart muscle, the development of injury potentials of rest and activity has been observed. When completely developed, the injury potential curve of activity is fundamentally monophasic in form and consists of only two parts: (1) a part in which the resting potential, negative with respect to uninjured resting muscle, is rapidly abolished and replaced by a potential positive with respect to the same reference, and (2) a slower and continued decline of the potential to the resting state. Modifications in this curve causing it to depart from this strictly monophasic type may result from two factors, inclusion of action potentials from uninjured regions of the muscle and from incomplete or nonuniform injury. The former occur most prominently in bipolar leads, are less often present in unipolar leads, and are usually absent in coaxial leads. The latter effects are prominent during the development of suction injuries or during their subsidence and are always, in our experience, present in injury potential curves derived from burned or crushed regions.

It is shown by several experimental methods that the injury potential of activity is derived solely from the region of injury or the immediately contiguous tissue. The electrode on uninjured tissue contributes to the recorded curve only by the addition of active potential components arising from the region of the electrode or from normal heart tissue intervening between the two electrodes. AUTHORS.

Wintrobe, M. M.: Relation of Nutritional Deficiency to Cardiac Dysfunction. Arch. Int. Med. 76: 341 (Nov.-Dec.) 1945.

This article contains a good summary of the cardiac effects of nutritional deficiency. The author reviews the literature on the subject from the clinical and experimental standpoints and reports his own experiments upon the production of thiamine deficiency in pigs. The effects of avitaminoses, particularly of vitamin B_1, are discussed from the clinical, electrocardiographic, and pathologic standpoints. BELLET.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.